Sex and Gender Perspective in Lung Cancer: State of the Art

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ICAPEM Meeting, November 7 2024
Madrid, Spain

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Lung Cancer in Women: Growing Trends, Unmet Needs

The New York Times

Younger Women Are Getting Lung Cancer at Higher Rates Than Men

Researchers are struggling to understand what is driving the gender disparity in lung cancer cases among people 35 to 54.

Getty Images

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Lung Cancer in Women

Jyoti D. Patel

Lung Cancer in Women: The Past, Present, and Future

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The role of sex and gender in the diagnosis and treatment of lung cancer: the 6th ICAPEM Annual Symposium

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Sex and Gender in Lung Cancer

- Lung Cancer Incidence and Biology
- Lung Cancer Patient Pathway
- Treatment and Outcomes
- Clinical Trials

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Presenter Name
Title, Department

Sex and Gender in Lung Cancer

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Lung Cancer Biology

- Biological factors, hormonal differences, environmental and occupational exposures

Tobacco/ Cigarette Smoking:

- Women who smoke 25 x more likely to die from lung cancer vs never smokers
- Quitting smoking at any age lowers risk in women
- Female smokers at greater lung cancer risk vs men with equal cigarette exposure
- ?Female sex hormones play a carcinogenesis

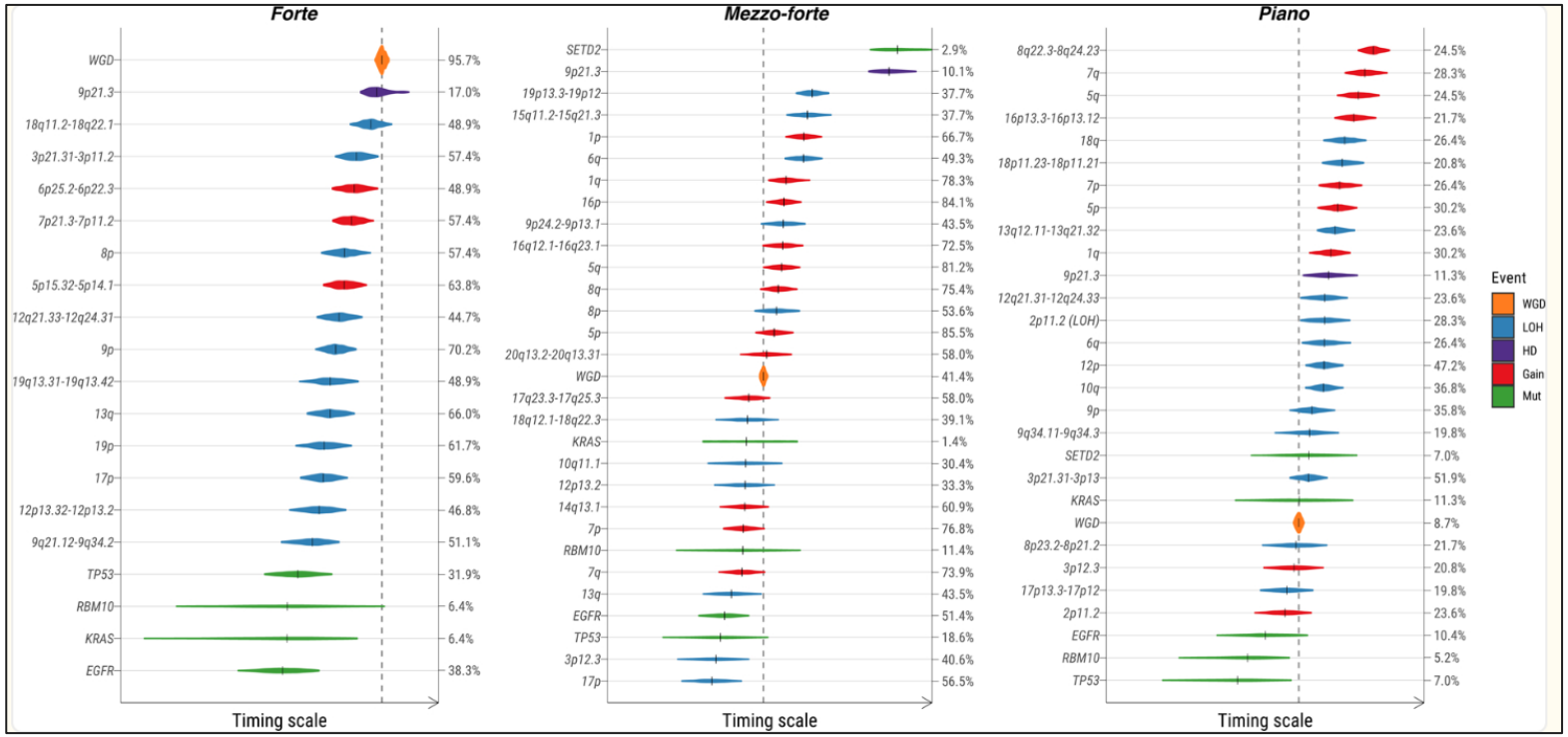
Never Smokers

- Lung adenocarcinomas in NS's have a distinct biology, more common in women
- Lung cancer incidence in Asia/China similar to western world, different rf's
- Greater proportion of EGFR+ NSCLC in Asia
- Emerging role of indoor pollutants/cooking index

Presenter Name
Title, Department

Thun et al, NEJM 2013, Jha et al NEJM 2013, De Matteis Am J Epidemiol 2013, Transl Oncol 2019; Felip et al, ESMO 2022

Lung Cancer in Never Smokers has a distinct biology



- WGS in tumor & matched normal
- 232 never smokers (189 adeno, 75.4% female)

<u>Three subtypes</u>:

- **Piano**: somatic UBA1 mutations, germline variants, stem cell-like properties, low TMB, high ITH, long telomeres, KRAS mutations
- **Mezzo-forte**: EGFR mutations, amplifications
- **Forte**: Whole genome doubling

Zhang et al, Nature Genetics 2021; Felip et al, ESMO 2022

Lung Cancer Incidence in Never Smokers

Population	Study Name	Sample size
N America	Florida Cancer Data Systems	77,641 patients
N America	Nurses Health Study	5379 patients
N America	Health Professionals Follow up Study	
N America	California Teachers Study	
N America	Multiethnic Cohort Study	
N America	First National Health and Nutrition Examination Survey	
N America	Epidemiologic Follow Up Study	
UK	Health Improvement Network IQVIA	399,3599 patients
Greece	Cancer Registry of Crete	5509 patients
France	French National Institute of Statistics	346,173 patients
Sweden	Swedish Lung Cancer Registry	523 patients
Finland	METCA project: University of Helsinki	106,193 patients
Taiwan	Taiwan Cancer Registry, Taiwan Biobank, TCRLF, NHIRD, MBIS, National Health Interview Study	61,285 patients
Korea	Korean National Health Insurance Service	656,9144 patients
China	China National Lung Cancer Screening Program	794,283 patients
International	22 cancer registry cohort	630,000 patients

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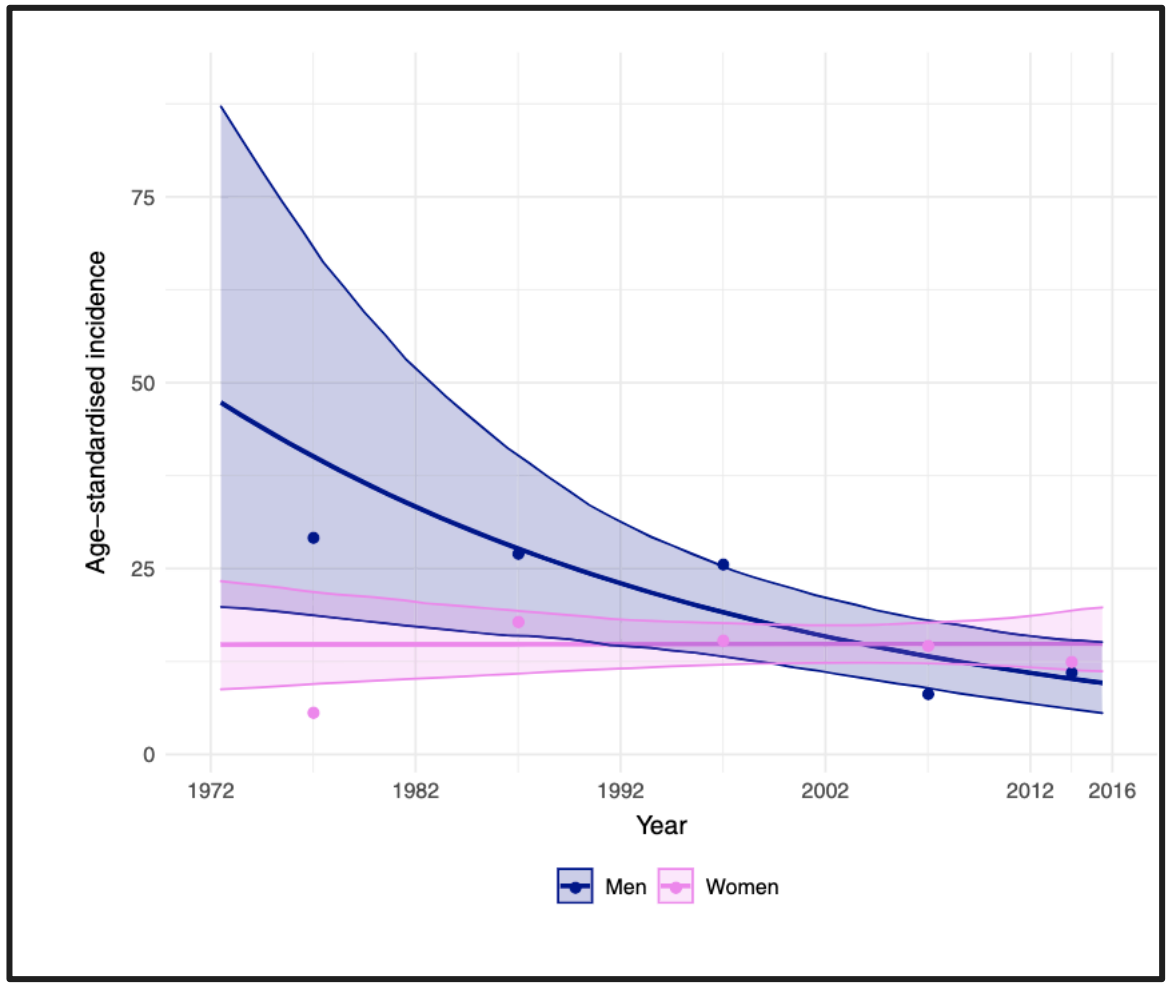
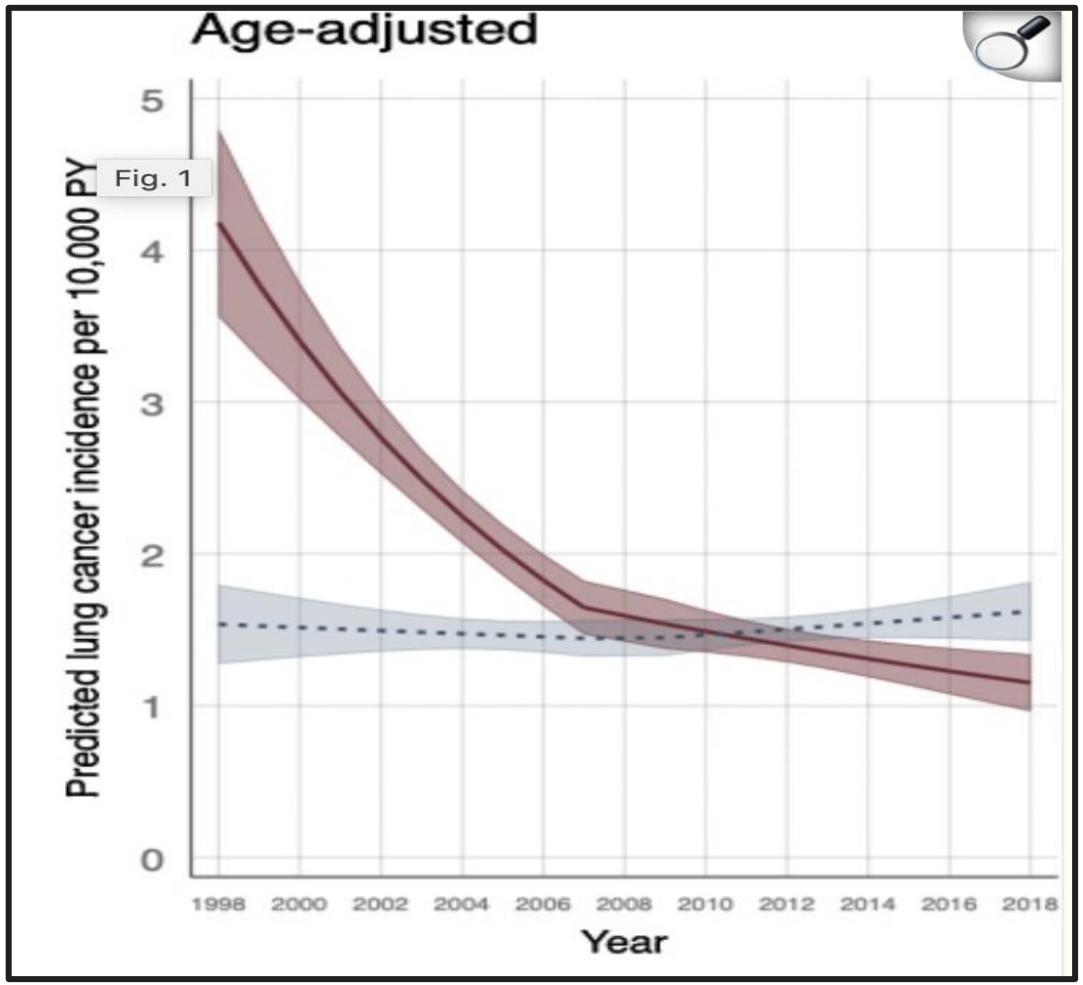
Lung Cancer incidence in Never Smokers: Decreasing in men, Stable in women





- In Finland (1972–2015) LC incidence significantly decreased in men, remained stable for women

- In the UK, AAIRs declined for men, AAIRs remained stable for women

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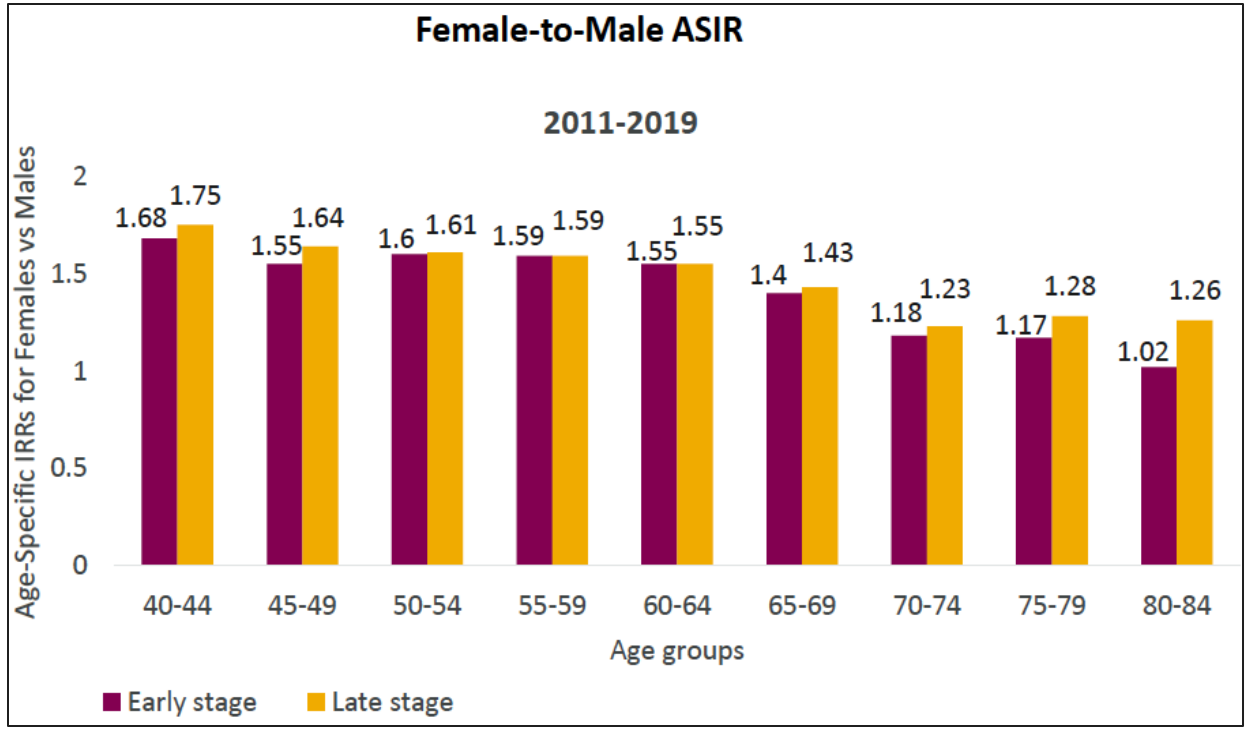
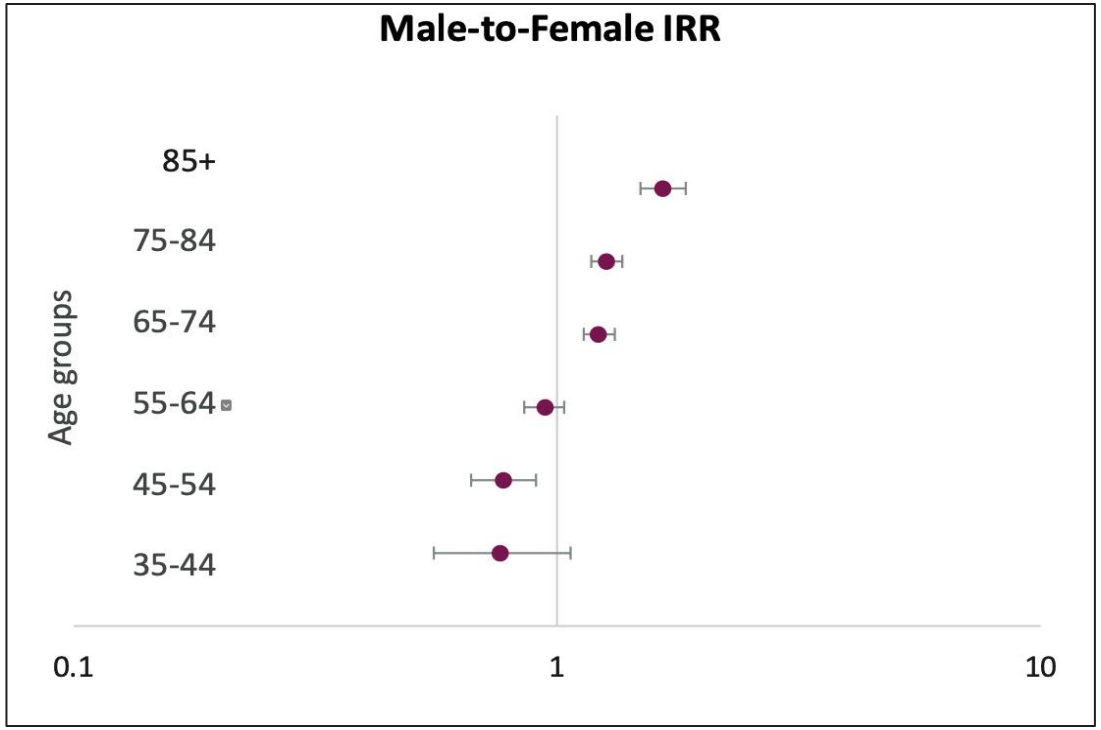
Younger women have a higher incidence of LC compared with men





- In Taiwan (2011-2019) females had higher rates of all stage LC than men across all age groups, except 65-69 where rates were similar, & 75-84- lower late stage

- Women 45-54 years higher IRR than men
- Women aged 65+ years have lower IRR than men

Adenocarcinomas more common in female v male never smokers

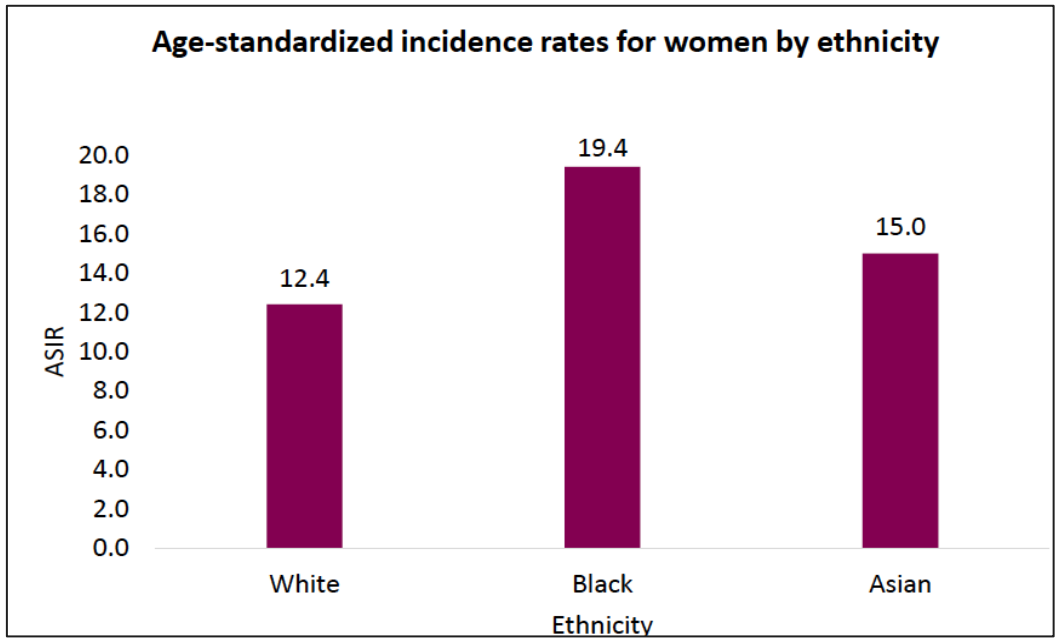
Study	Sample size	Proportion of Incident cases Adenocarcinoma in Women (%)	Proportion of Incident cases Adenocarcinoma in Men (%)
Wakelee, et al USA/Sweden	5379 patients	70	67
Rissanen, et al Finland	106 193 patients	38.7	29.8
Wu, et al China	794 283 patients	56.9	33.8
Chien, et al Taiwan	61 285 patients	53.2	46.8

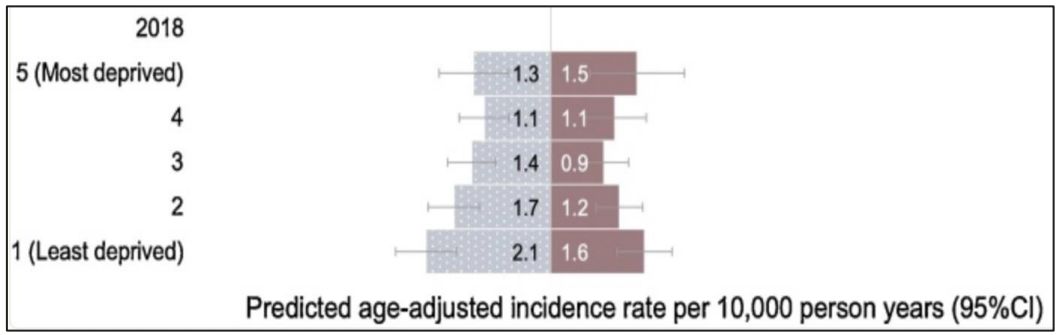
- In Finland (1972-2015) the incidence of adenocarcinoma among women significantly increased over time (AAPC: 2.83% [95% CI 0.03% to 5.71%], p=0.043)

- In men the trend was not significant (AAPC: -0.62% [95% CI -6.64 to - 5.79], p=0.847)

Wakelee et al, J Clin Oncol 2007; Rissanen et al, Int J Cancer 2021; Wu et al, Chin Med J 2022; Chien et al JAMA Netw Open 2023

Least socially deprived black & Asian women have higher incidence of LC





- An international pooled analysis of 22 cancer registries and 13 cohorts, >630,000 pts showed Black and Asian women had higher rates of lung cancer vs. Caucasian women
- Recapitulated in a US study
- A study from the UK showed AAIRs increased by 5% per year (95 %CI: 2–9%) for women in the least social deprived areas

Thun et al, PLOS MED 2008; Pinheiro et al, Cancer Epidemiol 2020; Rait and Horsfall et al, Cancer Epidemiol 20

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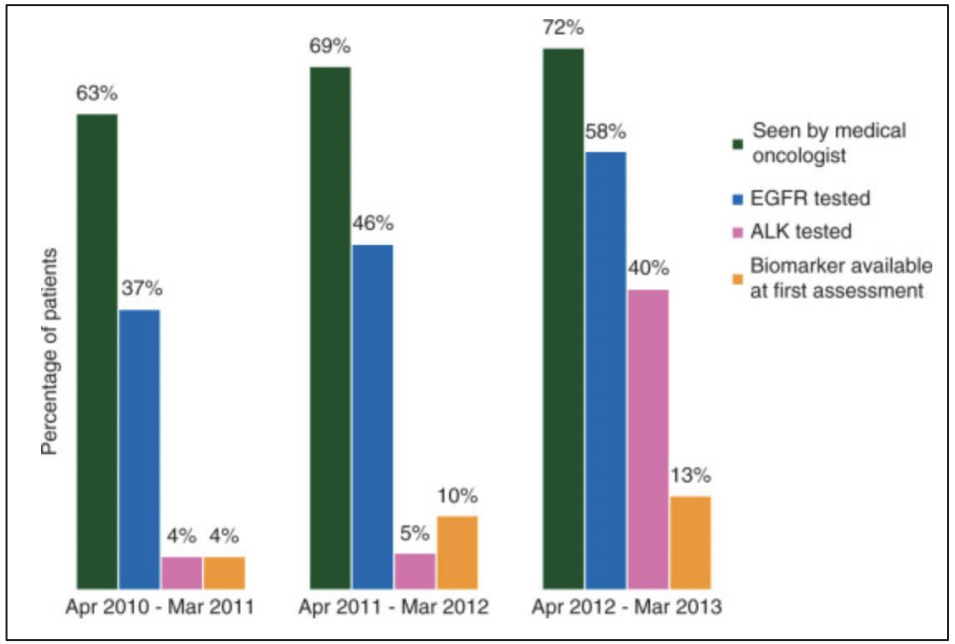
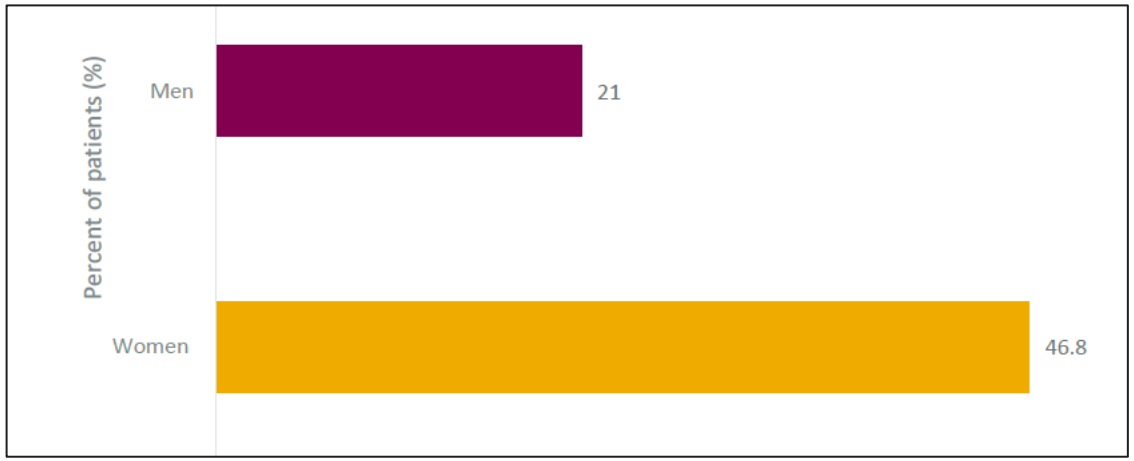
Disparities in Biomarker Testing in Lung Cancer may favour females

Population	Study Name	Sample size
Canada, 2015	Princess Margaret Cancer Centre	300 patients
N America, 2021	Flatiron Health Electronic Database	11409 patients





- Patients with NSCLC who underwent biomarker testing (EGFR/ALK)
- Females were more likely then males to have testing 46.8% v 21%, p=0.002)
- Male patients were less likely than females to have ROS1 testing (OR 1.11, p<0.0001)

Lim et al, Ann Oncol 2015; Wong et al, Clin Lung Cancer 2021

Time to treatment initiation faster in men vs. women

Population	Study Name	Cohort Type	Sample size
N America	Boston Medical Centre study	Retrospective	687 patients
N America	NLST, National Lung Cancer Screening Trial	Prospective	14,000 patients
N America	SEER Database	Retrospective	22,145 patients
N America	University Hospitals + SEER Database	Retrospective	733,927 patients
Brazil	ONCO15 National Database	Retrospective	4789 patients
Spain	NR	Retrospective	892 patients

- Several studies have evaluated time to treatment by gender

- Reported outcomes include:
  - time from diagnosis to treatment (n=2)
  - time from test to treatment (n=1)
  - time to treatment unspecified (n=3).

Selected studies show time to treatment shorter in men

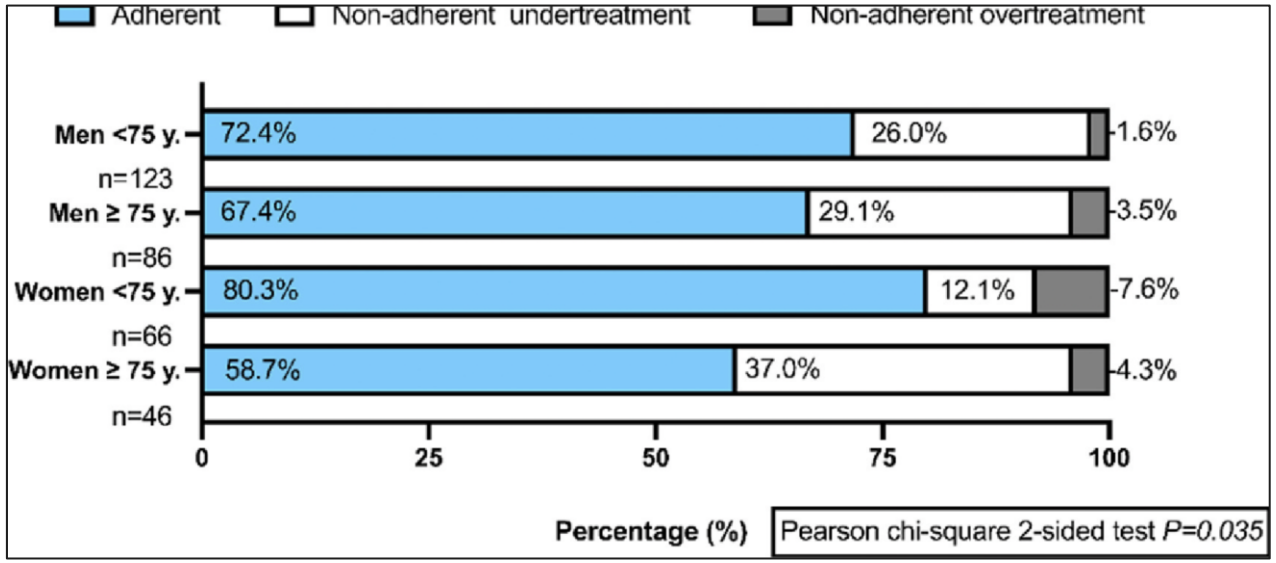
Author, year	Outcome measure	Stage of Disease	Gender analysis Men	Gender analysis Women	Sample size	Measure	Outcome
Siddiqui et al, 2023	Time from image to treatment	Not specified	More likely		687	Time	Men 72 days Women 87 days
Souza et al, 2022	Time from diagnosis to treatment	Stage IV	More likely		4789	OR	Men 1.22 Women NR
Sesti et al, 2020	Time from diagnosis to follow up	Not specified		More likely	14,000	OR	Women 1.23
Chilet-Rosell et al, 2020	Time from SPN diagnosis to treatment	Not specified		More likely	892	RR	Women 1.8 (CXR) Women 4.2 (CT)
Shugarman et al, 2009	Time to treatment (unspecified)	Stage III		More likely	4789	OR	Women 1.3
Stabellini et al, 2022	Time from diagnosis to treatment	Stage IV	More likely		733,927	% of cohort	Men 57% Women 51.8%

- In USA, Stabellini (2022) showed females with advanced stages (III–IV) waited significantly longer than men to receive chemotherapy after diagnosis (48.2% vs 43% receiving treatment >30 days p = 0.02)
- In the remaining studies, males initiated treatment quicker on average after a suspicious image was detected and were also more likely to initiate treatment within 60 days of diagnosis.

Guideline-based care has gender differences

Population	Study Name	'Guideline-concordant'	Sample size
N America	North Caroline Lung Screening Registry	Adherence to Lung RADS	685 patients
N America	National Cancer Database	Adherence to stage III guideline	45,825 patients
N America	SEER Database	Adherence to NSCLC guideline	22,145 patients
N America	National Cancer Database	Adherence to stage I guideline	241,146 patients
Finland	Vassa Hospital, Finland	Adherence to NSCLC guideline	418 patients

Older women had less guideline concordant care



- Finnish study of 321 pts examined guideline based care by age and gender
- Identified non-adherence to NSCLC treatment guidelines was:
  - highest in ≥75-year-old women (41.3%)
  - lowest in women <75-year-old (19.7%) (p = 0.035)

- Undertreatment was more common in men
- Overtreatment was more common in women

- Women with stage 1 (OR: 1.08; 95% CI: 1.03,1.14; p=0.002) and stage 3a-3b LC (OR: 0.93; 95% CI: 0.91–0.96; p<0.001) were less likely to receive guideline concordant care

Paakkola et al, Cancer Treat Res Comms 2023

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Immunotherapy outcomes are impacted by gender

First Author	Study Type	Journal	Sample size
Conforti et al	Systematic Review & Meta-Analysis	Lancet Oncol, 2019	11351 patients
Conforti et al	Systematic Review & Meta-Analysis	J Natl Cancer Inst 2018	4923, 3974 patients
Confort et al	Prospective Cohort, Translational	Clin Cancer Res, 2021	329, 391 patients
Scott et al	Prospective Cohort, Translational	Frontiers Oncoi, 2022	89 patients
Unger et al	Systematic Review & Meta-Analysis	J Clin Oncol, 2022	23296 patients

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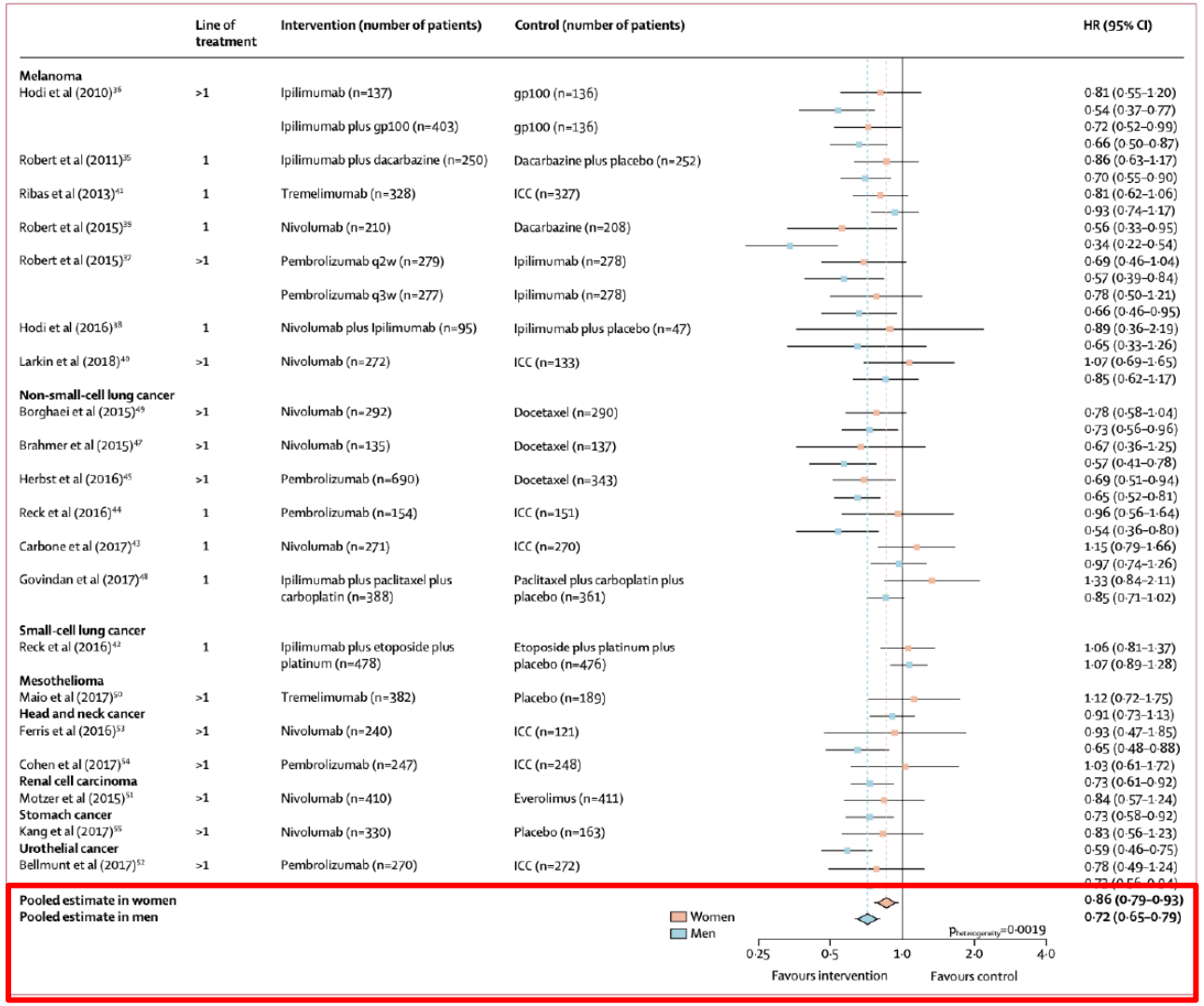
Differential outcomes from immunotherapy by gender



Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis

Fabio Conforti, Laura Pala, Vincenzo Bagnardi, Tommaso De Pas, Marco Martinetti, Giuseppe Viale, Richard D Gelber, Aron Goldhirsch

Pooled OS HR:

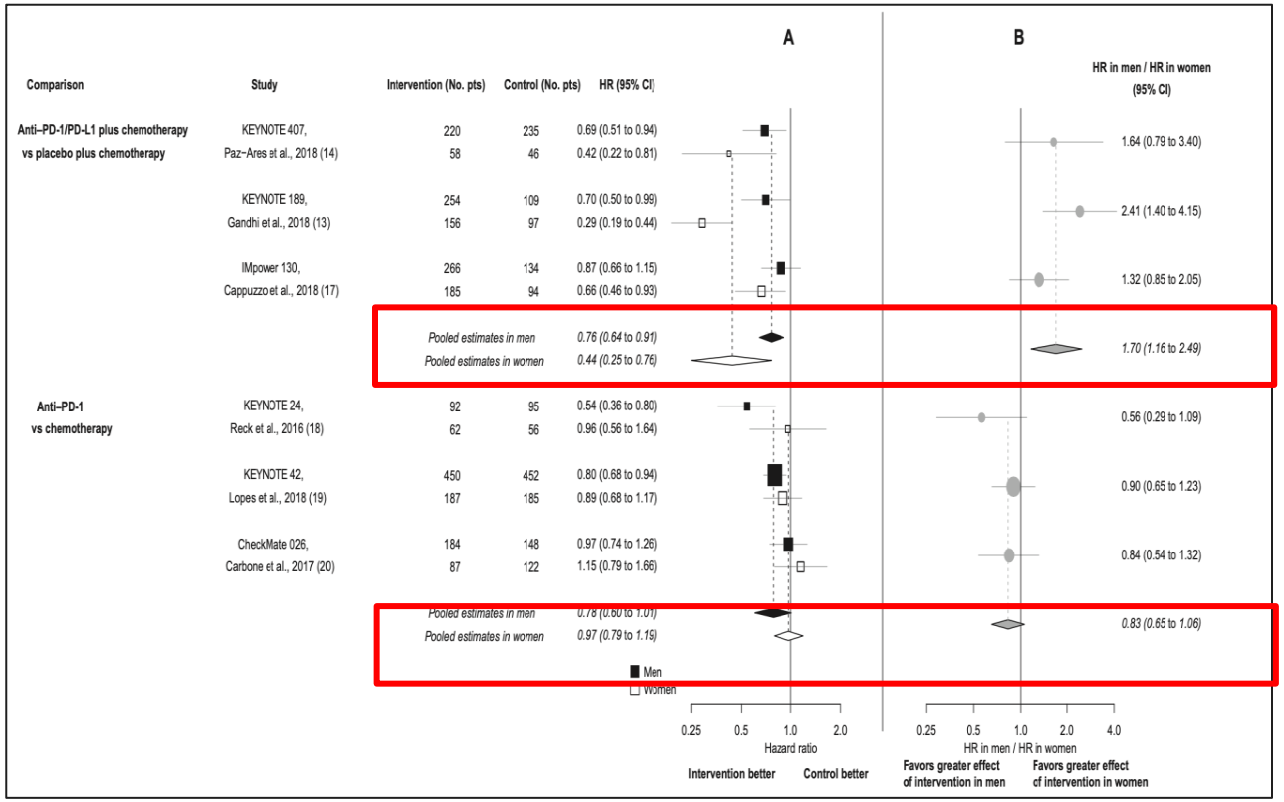
-Males: 0·72 ICIs v, control groups
-Women 0·86 ICIs v control groups

-Difference in efficacy men v women treated with ICIs significant (p=0·0019)

- 31% NSCLC, 32% melanoma

Conforti et aL, Lancet Oncol 2018

Differential outcomes of chemo-immunotherapy by gender



Conforti et aL, J Natl Cancer Inst 2018

Sex-Based Heterogeneity in Response to Lung Cancer Immunotherapy: A Systematic Review and Meta-Analysis

Fabio Conforti, Laura Pala, Vincenzo Bagnardi, Giuseppe Viale, Tommaso De Pas, Eleonora Pagan, Elisabetta Pennacchioli, Emilia Cocorocchio, Pier Francesco Ferrucci,

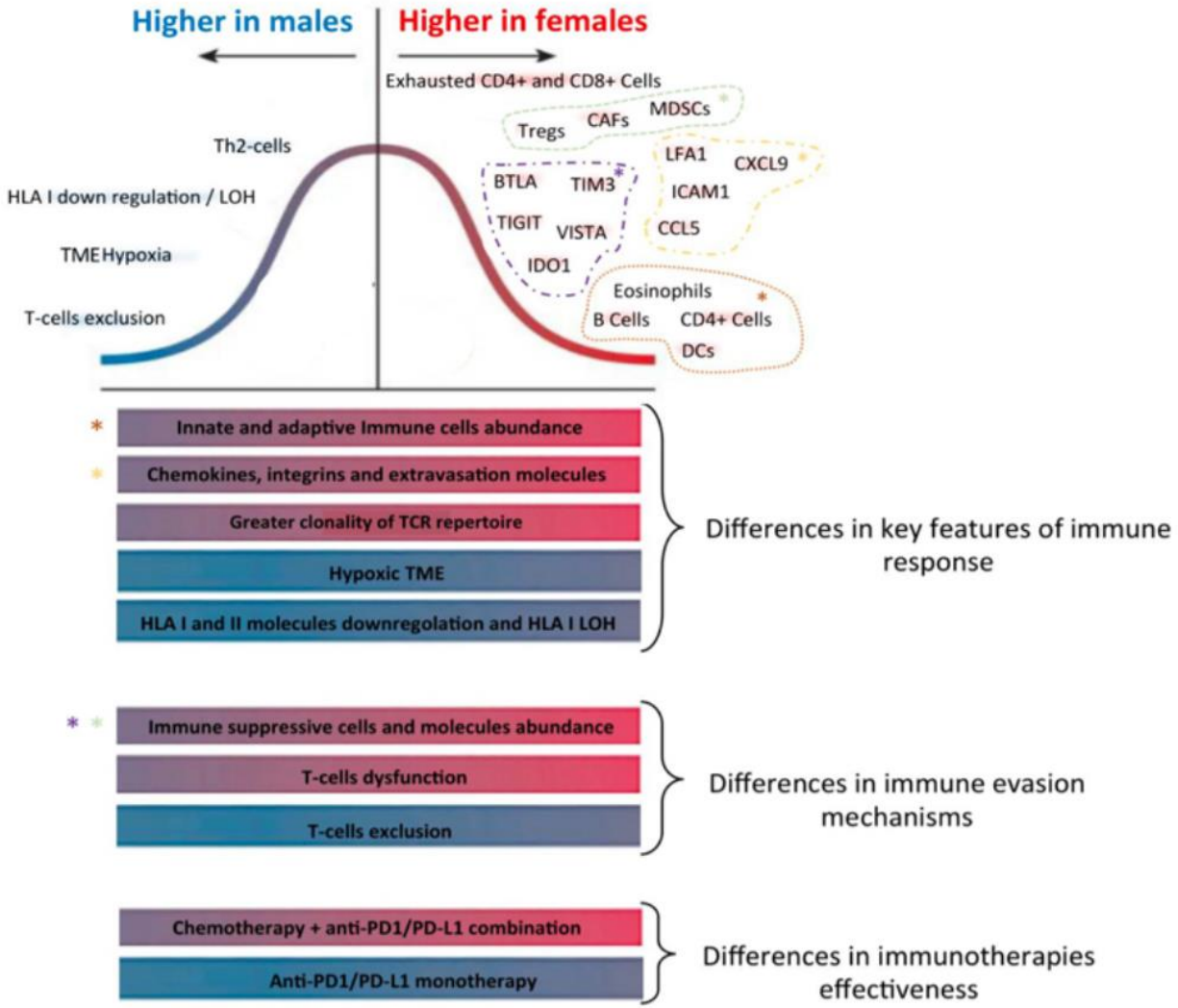
8 RCT Meta-analysis, Pooled OS HR:

- anti-PD-1/PD-L1 + chemo vs chemo
- Men: 0.76
- Women: 0.48
- Pooled ratio OS HRs m vs w 1.56, greater effect for women

6 RCT Meta-analysis, Pooled OS HR:

- anti-PD-1 alone v anti-PD-1/PD-L1 + chemotherapy.
- Men: 0.78
- Women: 0.97 anti-PD-1 alone
- Pooled ratio of OS HRs 0.83, greater effect in men

Biology of Immune Evasion & IO biomarker association differs by gender



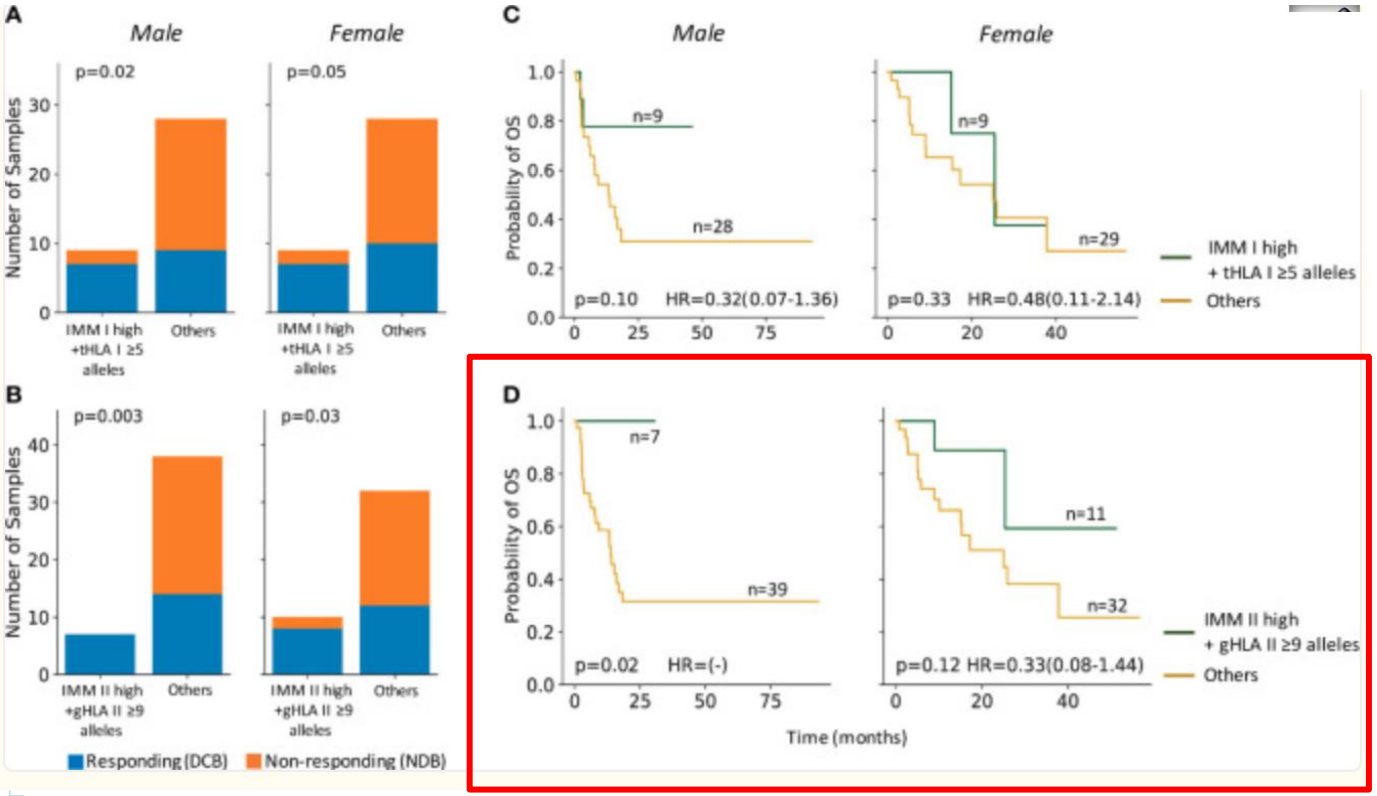
(i) Transcriptome data 2575 early-stage NSCLCs, 7 datasets
(ii) 327 tumor samples from TRACERx
(iii) Two independent cohorts of 329 and 391 patients, advanced NSCLC treated with anti-PD-(L)1

TME of females
- greater T-cell dysfunction, higher abundance of immune-suppressive cells (CAFs, MDSCs, Tregs)

TME of males
- T-cell-excluded phenotype
- Impaired neoantigen presentation
- Sex-based differences in TMB association with outcome to anti-PD(L) in NSCLC patient cohorts

Conforti et aL, Clin Cancer Res 2021

Sex-specific immunogenomic features determine response to IO



- WES data, HLA genotypes 482 NSCLC tumors (TCGA)
- WES data from 89 patients with NSCLC treated with ICI

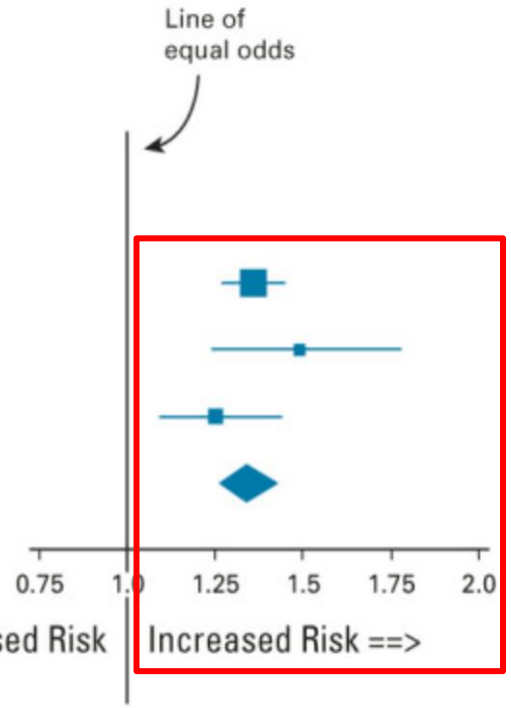
- **In women:**
  - TMB (p=0.005), class I immunogenic missense mutation load (p=0.005), class II immunogenic missense mutation load (p=0.004), mutational smoking signature (p<0.001) assoc with ICI response

- **In men:**
  - No assoc with these features and ICI outcome

Scott, Naidoo et al, Frontiers Oncol 2022

Sex-specific differences in toxicity from anti-cancer therapy

Treatment Domain	Female *v* Male, % of Severe AEs	OR (95% CI)	*P*
Chemotherapy	73.9 *v* 67.6	1.36 (1.27 to 1.45)	< .001
Immunotherapy	56.6 *v* 48.8	1.49 (1.24 to 1.78)	< .001
Targeted therapy	50.0 *v* 44.8	1.25 (1.09 to 1.44)	.001
Overall	68.6 *v* 62.2	1.34 (1.27 to 1.42)	< .001



- 23,296 patients from 202 trials
  - Women, 37.9%; men, 62.1%
  - 274,688 AEs: 17,417 from CT, 2319 from IO, 3560 from targeted therapy
- 64.6% has a grade 3+ AE
- **In Women:**
- 34% increased risk of severe AEs v men
- 49% increased risk of an irAE v men
- Increased risk of severe hematologic AE from chemotherapy or immunotherapy

Unger et aL, J Clin Oncol 2022

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Gender Disparity Exists in Lung Cancer Clinical Trials

First Author	Study Type	First Author, Journal, Year	Sample size
N America	NIH, SEER, US Census	Dymanus et al, Cancer 2021	59 988 patients
N America	NCI Cooperative Group	Murthy et al, JAMA 2004	75 215 patients
Netherlands, Belgium	NELSON trials group	Yousaf-Khan et al, J Thoracic Oncol 2015	606 409 patients
International	Pubmed pooled analysis	Aslam et al, Cancer Rep 2023	426 clinical trials

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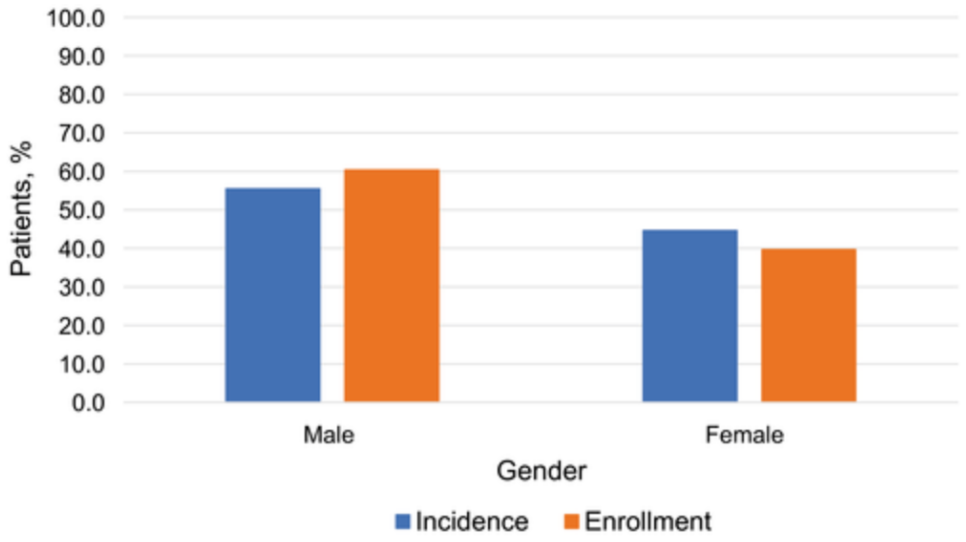
Women are underrepresented in Lung Cancer Clinical Trials



- Pooled analysis of 149 clinical trials from 2006-2019
- 60.3% and 39.7% were male and female
- Leading to 127 oncology drug approvals
- US incidence rates 55.4% for men, 44.6% for women.

- Gender representation varied by specific tumor type

- **Enrolment incidence disparity*** (EID=3.2; p = NR), men overrepresented in lung cancer clinical trials compared to the incidence among men

- Overall, women were underrepresented when compared with expected incidence (EID, +4.9%; 42% of trials)

Dymanus et al, Cancer 2021

Women are underrepresented in Lung Cancer Clinical Trials I

June 9, 2004

Participation in Cancer Clinical Trials
Race-, Sex-, and Age-Based Disparities

Vivek H. Murthy, MD, MBA; Harlan M. Krumholz, MD, SM; Cary P. Gross, MD

» Author Affiliations

JAMA. 2004;291(22):2720-2726. doi:10.1001/jama.291.22.2720

- Cross sectional population analysis of therapeutic NCI analysis from 2000-2002:
- **Enrollment fraction**: number of trial enrollees divided by US cancer cases in each race and age subgroup
- Men had higher clinical trial enrolment fractions than women (0.9% vs 0.7%; OR: 1.23; p <.001)
- Men were more likely to enroll in lung cancer trials v women (enrollment fractions: 0.9% vs 0.7%, p<0.001)

Table 4. Trial Enrollment Fraction According to Age and Sex, 2000-2002

Type of Cancer and Age Group, y	Males		Females		Odds of Enrollment, Males:Females	
	No. of Trial Participants	Enrollment Fraction, %	No. of Trial Participants	Enrollment Fraction, %	Odds Ratio (95% CI)	*P* Value
Colorectal						
All	4750	2.1	3684	1.6	1.30 (1.24-1.35)	<.001
30-64	2862	3.9	2262	3.9	1.00 (0.95-1.06)	.90
65-74	1416	2.1	1022	1.8	1.18 (1.08-1.28)	<.001
≥75	472	0.6	400	0.4	1.54 (1.35-1.76)	<.001
Lung						
All	2606	0.9	1691	0.7	1.23 (1.16-1.31)	<.001
30-64	1345	1.3	1015	1.3	1.03 (0.95-1.12)	.47
65-74	949	0.9	518	0.6	1.40 (1.26-1.56)	<.001
≥75	312	0.3	158	0.2	1.71 (1.41-2.07)	<.001
Total	7356	1.4	5375	1.1	1.22 (1.17-1.26)	<.001

Murthy et al, JAMA 2004

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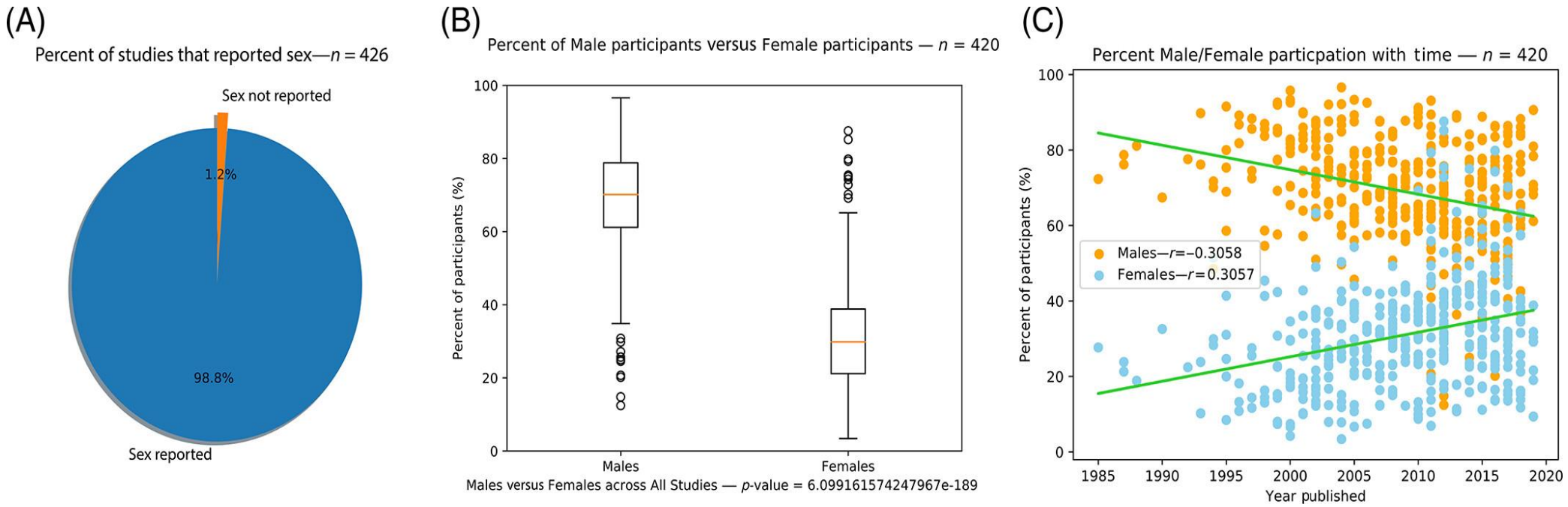
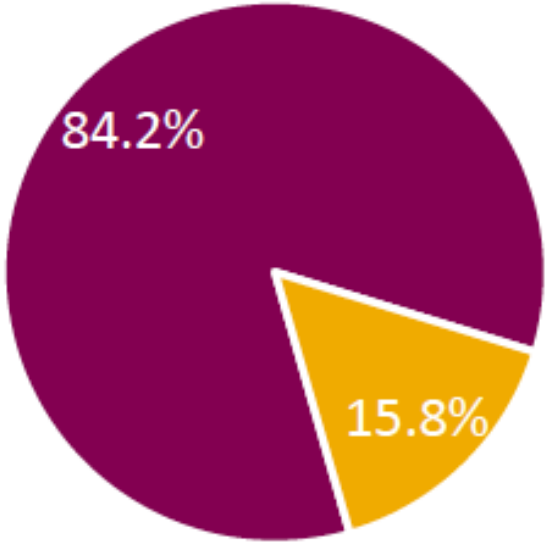
Women underrepresented in Lung Cancer Clinical Trials II

- Pooled analysis from 1984-2019
- 426 trials phase III lung cancer trials
- Male participation (69.02%) higher vs females (30.98%, p < 0.001)
- Female participation improved with time at a rate of 0.65% per year



Aslam et al, Cancer Rep 2023

Women dramatically underrepresented in Lung Cancer Screening Trials



- In the NELSON lung cancer screening trial:
- Significantly more men participated vs. women
- 84.2% vs 15.8%, p<0.001

Trial	Country	Criteria	Reduction in Mortality
NELSON	Europe	Age: 50-80 years Smoking: <20 pack-yrs\	↓26%
NLST	USA	Age: 55-75 years Smoking: <15 pack-yrs	↓20%

TABLE 1. Baseline Characteristics of NELSON Control Group Participants and Eligible Nonresponders

	Control Group Participants		Eligible Nonresponders		*p* Value
	Total *N* = 7453		Total *N* = 13,661		
	%	*n/N*	%	*n/N*	
Age (years): median (IQR)	57.0 (8.0)	7453	58.0 (9.0)	13,661	<0.001
Male	84.2	6275/7453	80.6	11,013/13,661	<0.001

Yousaf-Khan et al, J Thoracic Oncol 2015

Expanding Lung Cancer Screening in Europe

Strengthen the Screening **o**f **L**ung **C**ancer in **E**urope (SOLACE)

3 year duration , 32 beneficiaries, 2 associated partners

WP1: Project management and coordination
WP2: Knowledge Hub
WP3: Implementation network

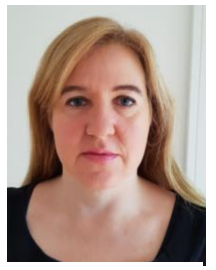
WP4: Pilot 1: Enhancing female participation
WP5: Pilot 2: Recruitment hard-to-reach individuals
WP6: Pilot 3: High risk populations

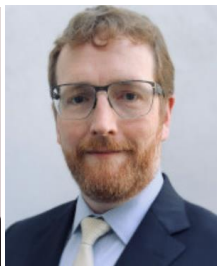
WP7: Evaluation, sustainability and training
WP8: Dissemination and outreach

Lung Health Check Pilot Trial

- Manchester Lung Health Check Mobile Model
- ERS SOLACE Consortium
  (15-person Steering committee)
- LDCT scanning 5 days/week over 2 years
- Cases discussed at Beaumont Lung MDT

LUNG HEALTH CHECK | BEAUMONT RCSI CANCER CENTRE | Proudly funded by Irish Cancer Society

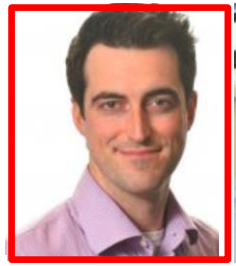




Program Management
C Noonan; S.Roche

Respiratory Medicine
D Ryan; I Counihan; R Morgan; E O'Brien

Surgery
G.Fitzmaurice; V Young



GP
P. Redmond

Clinical Trials
K Egan; **J Naidoo**

Radiology
J Ryan

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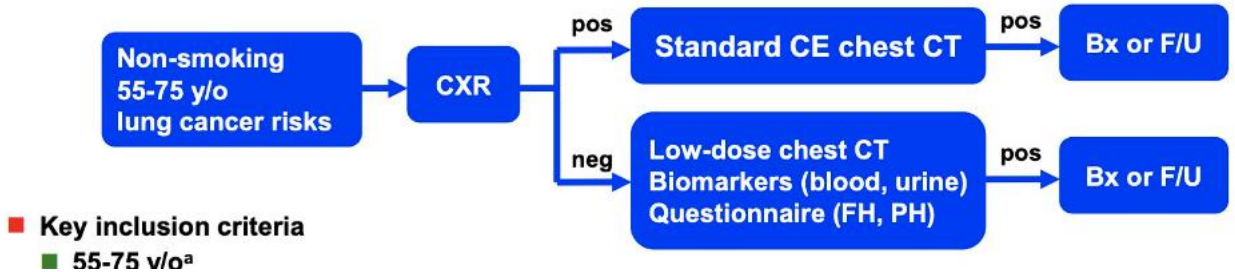
Lung Cancer Screening in Never Smokers:
Female Gender is a risk factor



TALENT trial:
- Multicentre, prospective study 17 centres in Taiwan

Eligible individuals:
- negative chest radiography
- Age\ 55–75 years
- never smoked/<10 pack-years
- Either: family history lung cancer; passive smoke; history pulmonary TB/COPD; cooking index>110; cooking without ventilation

Primary Outcome:
- Lung Cancer Detection rate

Results:
- 12011 participants, 2.6% LC detection rate
- Risk factors: **female sex**, age >60, family history

Chang et al, Lancet Respir Med 2024; Chyr et al IASLC WCLC 2023

Sex & Gender and Lung Cancer

Incidence and Biology

- Women are more susceptible to lung cancer via smoking
- Never smokers who develop lung cancer are predominantly women
- Increasing incidence in younger women, and the in less socially deprived by race

Pathway of care

- Gender differences in access to biomarker testing, time to treatment, and guideline based care

Treatment

- Outcomes to immunotherapy differ by gender, both efficacy and safety, due to biologic differences

Clinical Trials

- Gender disparity favoring men in participation in lung cancer clinical trials, including screening
- Dedicated efforts are ongoing to improve the participation of women in clinical trials
- Refinement of screening criteria and approaches will enhance the promise of early detection

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