Impacte del gènere I el sexe a la prevenció, tractament i pronòstic del càncer de pulmó

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Cancer statistics 2020

Lung
Source: Globocan 2020

GCO

Number of new cases in 2020, both sexes, all ages

Breast
2 261 419 (11.7%)

Lung
2 206 771 (11.4%)

Colorectum
1 931 590 (10%)

Prostate
1 414 259 (7.3%)

Stomach
1 089 103 (5.6%)

Liver
905 677 (4.7%)

Cervix uteri
604 127 (3.1%)

Oesophagus
604 100 (3.1%)

Other cancers
8 275 743 (42.9%)

Total: 19 292 789 cases

Number of deaths in 2020, both sexes, all ages

Lung
1 796 144 (18%)

Colorectum
935 173 (9.4%)

Liver
830 180 (8.3%)

Stomach
768 793 (7.7%)

Breast
684 996 (6.9%)

Oesophagus
544 076 (5.5%)

Pancreas
466 003 (4.7%)

Prostate
375 304 (3.8%)

Other cancers
3 557 464 (35.7%)
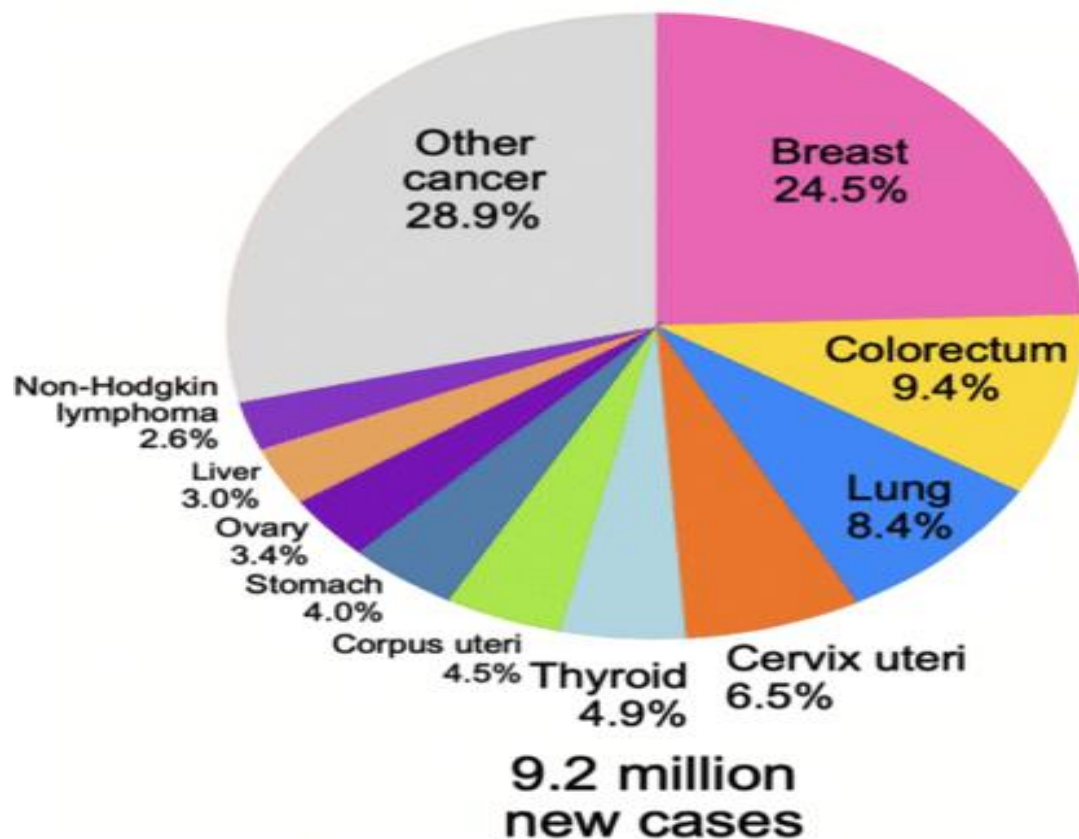
Total: 9 958 133 deaths
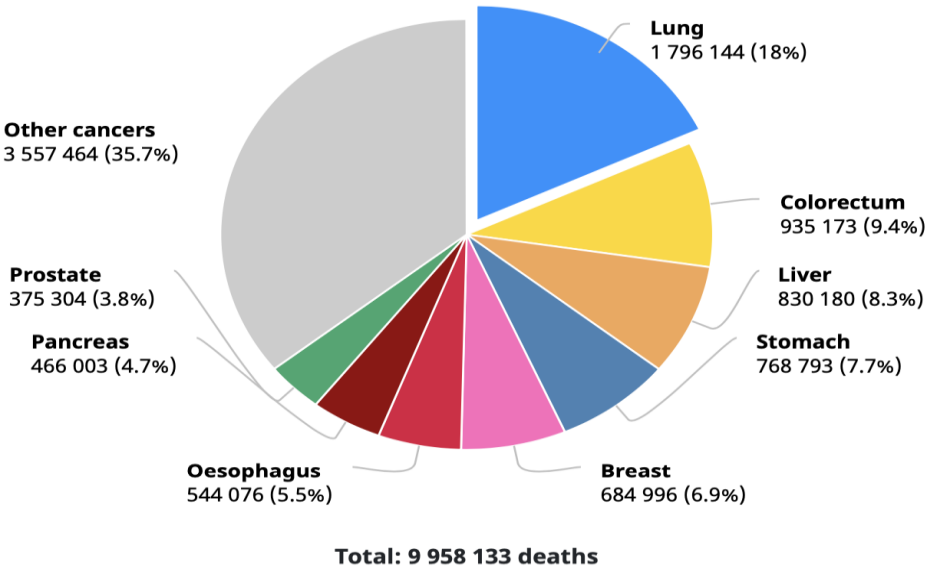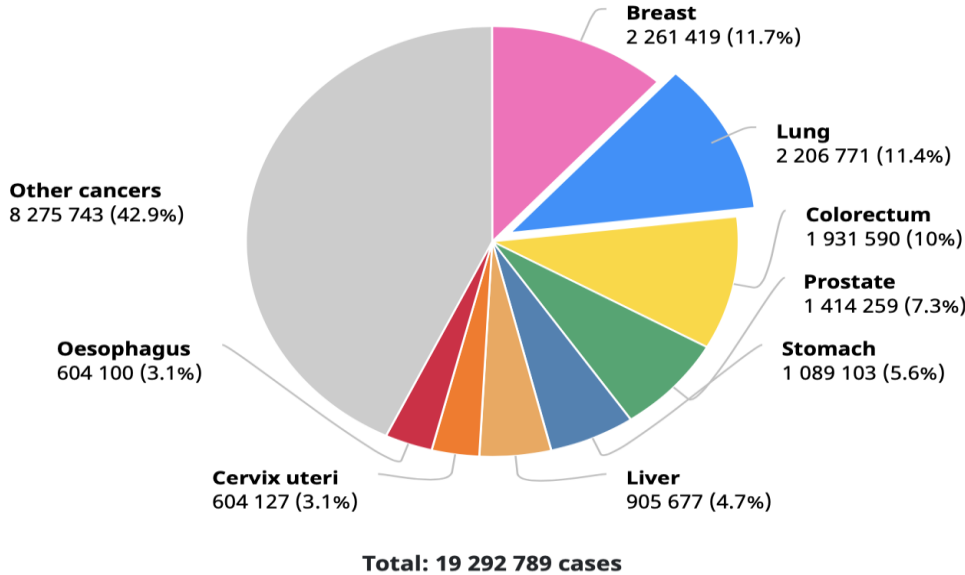
In both sexes combined, lung cancer is:

- The 2nd most commonly diagnosed cancer (2206771, 11.4% of total cases)
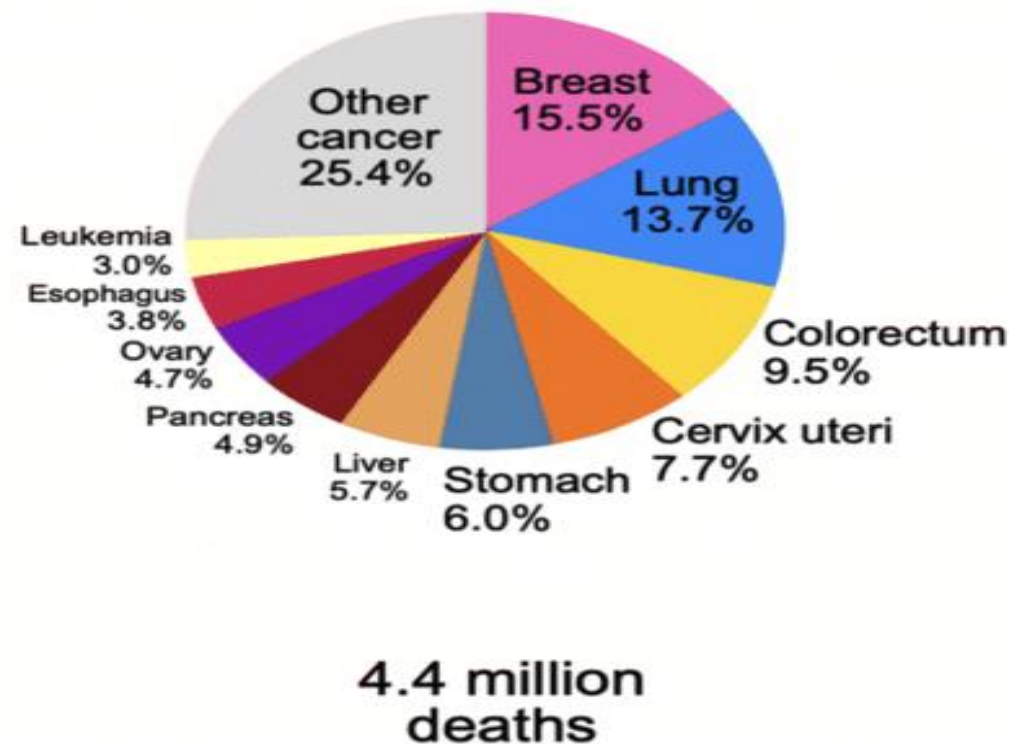- The leading cause of cancer death (1796144, 18% of total cancer deaths)

The 10 most common cancers in women 2020

Incidence

- Other cancer 28.9%
- Breast 24.5%
- Colorectum 9.4%
- Lung 8.4%
- Cervix uteri 6.5%
- Thyroid 4.9%
- Corpus uteri 4.5%
- Stomach 4.0%
- Ovary 3.4%
- Liver 3.0%
- Non-Hodgkin lymphoma 2.6%

9.2 million new cases

Mortality

- Other cancer 25.4%
- Breast 15.5%
- Lung 13.7%
- Colorectum 9.5%
- Cervix uteri 7.7%
- Stomach 6.0%
- Liver 5.7%
- Pancreas 4.9%
- Ovary 4.7%
- Esophagus 3.8%
- Leukemia 3.0%

4.4 million deaths

770828 lung cancer cases

607465 deaths due to lung cancer
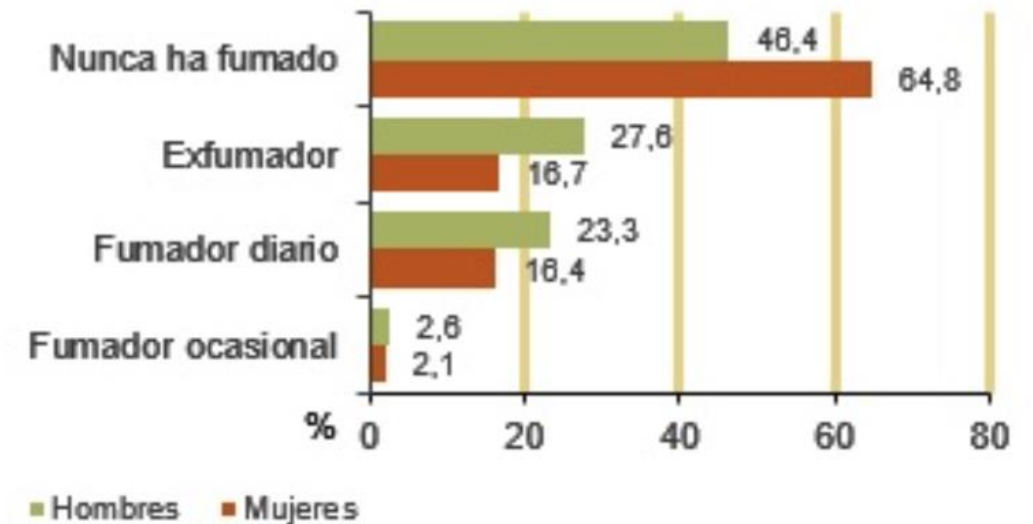
Sung CA CANCER J CLIN 2021

Cigarette smoking

- Two-thirds of lung cancer deaths worldwide are attributable to smoking *(Sung CA CANCER J CLIN 2021)*

- Women who smoke are ~25 times more likely to die from lung cancer than women who do not smoke *(Thun NEJM 2013)*

- Studies suggest female smokers are more likely to develop lung cancer compared to male when they smoke the same number of cigarettes *(De Matteis Am J Epidemiol 2013)*

- Controversy remains over whether female sex hormones play a role in the development of lung cancer regardless of smoking status *(Jin Translat Oncol 2019)*

INĒ
Instituto Nacional de Estadística

Consumo de tabaco. 2020

	Hombres	Mujeres
Nunca ha fumado	46,4	64,8
Exfumador	27,6	16,7
Fumador diario	23,3	16,4
Fumador ocasional	2,6	2,1

Fuente: Encuesta Europea de Salud en España 2020. INE-MSCBS

Region-specific incidence rates by sex for lung cancers in 2020

Lung

Region	Males	Females
Micronesia/Polynesia	51.6	22.9
Eastern Europe	49.0	11.6 -------| Hungary
Eastern Asia	48.1	22.1
Southern Europe	43.1	16.4
Western Asia	Turkey|-------- 41.7	8.7
Western Europe	41.7	25.0
Northern America	35.7	30.1
Northern Europe	33.3	26.8
Australia/New Zealand	28.1	22.7
Southern Africa	27.5	9.3
South-Eastern Asia	26.4	9.6
Caribbean	23.0	13.0
Northern Africa	19.5	3.5
South America	17.8	10.3
Melanesia	17.4	9.2
South Central Asia	9.7	3.5
Central America	6.8	4.0
Eastern Africa	4.2	3.0
Middle Africa	3.4	1.8
Western Africa	2.8	1.8

Age-standardized (W) incidence rate per 100,000

Males   Females

Among women the highest incidence rates are in Northern America, Northern and Western Europe, Micronesia/Polynesia, and Australia/New Zealand, with Hungary having the highest country-specific rates

Rates are also high in Eastern Asia, largely reflecting the high burden among Chinese women despite their low smoking prevalence

Lung cancer in never-smokers

- 10%-40% of lung cancers are diagnosed in never-smokers

- The most common histological subtype of lung cancer ADC

- The demographics of lung ADC in never-smokers are distinct compared with smokers, with a greater proportion of women, and Asian or Pacific islanders

- EGFR mutations, more frequent in women *vs* men

- Causative factors for lung cancer in never-smokers are poorly understood

Lung adenocarcinoma promotion by air pollutants

A complete understanding of how exposure to environmental substances promotes cancer formation is lacking. More than 70 years ago, tumorigenesis was proposed to occur in a two-step process: an initiating step that induces mutations in healthy cells, followed by a promoter step that triggers cancer development[1]. Here we propose that environmental particulate matter measuring 2.5 µm ($PM_{2.5}$), known to be associated with lung cancer risk, promotes lung cancer by acting on cells that harbour pre-existing oncogenic mutations in healthy lung tissue. Focusing on EGFR-driven lung cancer, which is more common in never-smokers or light smokers, we found a significant association between $PM_{2.5}$ levels and the incidence of lung cancer for 32,957 EGFR driven lung cancer cases in four within-country cohorts. Functional mouse models revealed that air pollutants cause an influx of macrophages into the lung and release of interleukin-1β. This process results in a progenitor-like cell state within EGFR mutant lung alveolar type II epithelial cells that fuels tumorigenesis. Ultradeep mutational profiling of histologically normal lung tissue from 295 individuals across 3 clinical cohorts revealed oncogenic EGFR and KRAS driver mutations in 18% and 53% of healthy tissue samples, respectively. These findings collectively support a tumour promoting role for $PM_{2.5}$ air pollutants and provide impetus for public health policy initiatives to address air pollution to reduce disease burden.
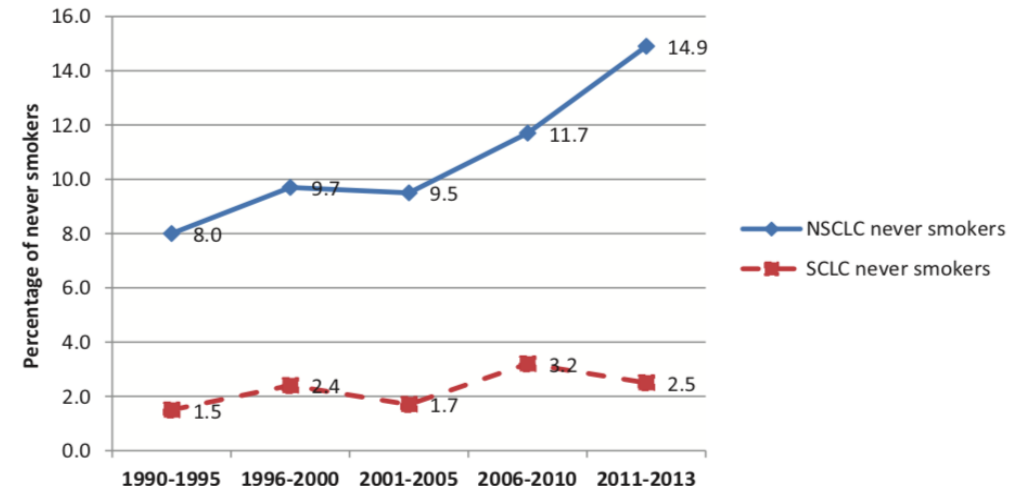
Is lung cancer incidence in never-smokers increasing?

Retrospective study using registries from 3 US Institutions (1990 to 2013)

Never-smoker NSCLC increased from 8.0% in 1990-95 to 14.9% in 2011-13 (P < .001)

Demographic	Smokers (n = 10 854 total NSCLC + SCLC)	Never smokers (n = 1249 total NSCLC + SCLC)	P*
Age, mean (SD), y			
NSCLC	63.4 (12.9)	60.6 (16.7)	<.001
SCLC	61.7 (12.2)	63.3 (14.7)	.44
Sex, No. (% of NSCLC cases)			
Female	3761 (82.5)	798 (17.5)	<.001
Male	5619 (93.1)	415 (6.9)	

*Two-sided P value from Student's t test for age and from chi-square test for sex.
NSCLC = non–small cell lung cancer; SCLC = small cell lung cancer.

No. of patients	1990-1995	1996-2000	2001-2005	2006-2010	2011-2013	
All NSCLC	677	1726	2391	3182	2617	
Never smoker NSCLC	54	168	228	372	391	P<0.001
All SCLC	136	297	356	404	317	
Never smoker SCLC	2	7	6	13	8	P=0.36

Pelosof JNCI 2017

Higher lung cancer incidence in young women than young men (US)

- Nationwide population-based incidence of lung cancer: 1995 – 2014

- Among persons born since the mid-1960s, incidence rates of lung cancer significantly higher among young women than among men

- Patterns not fully explained by sex differences in smoking behaviors)
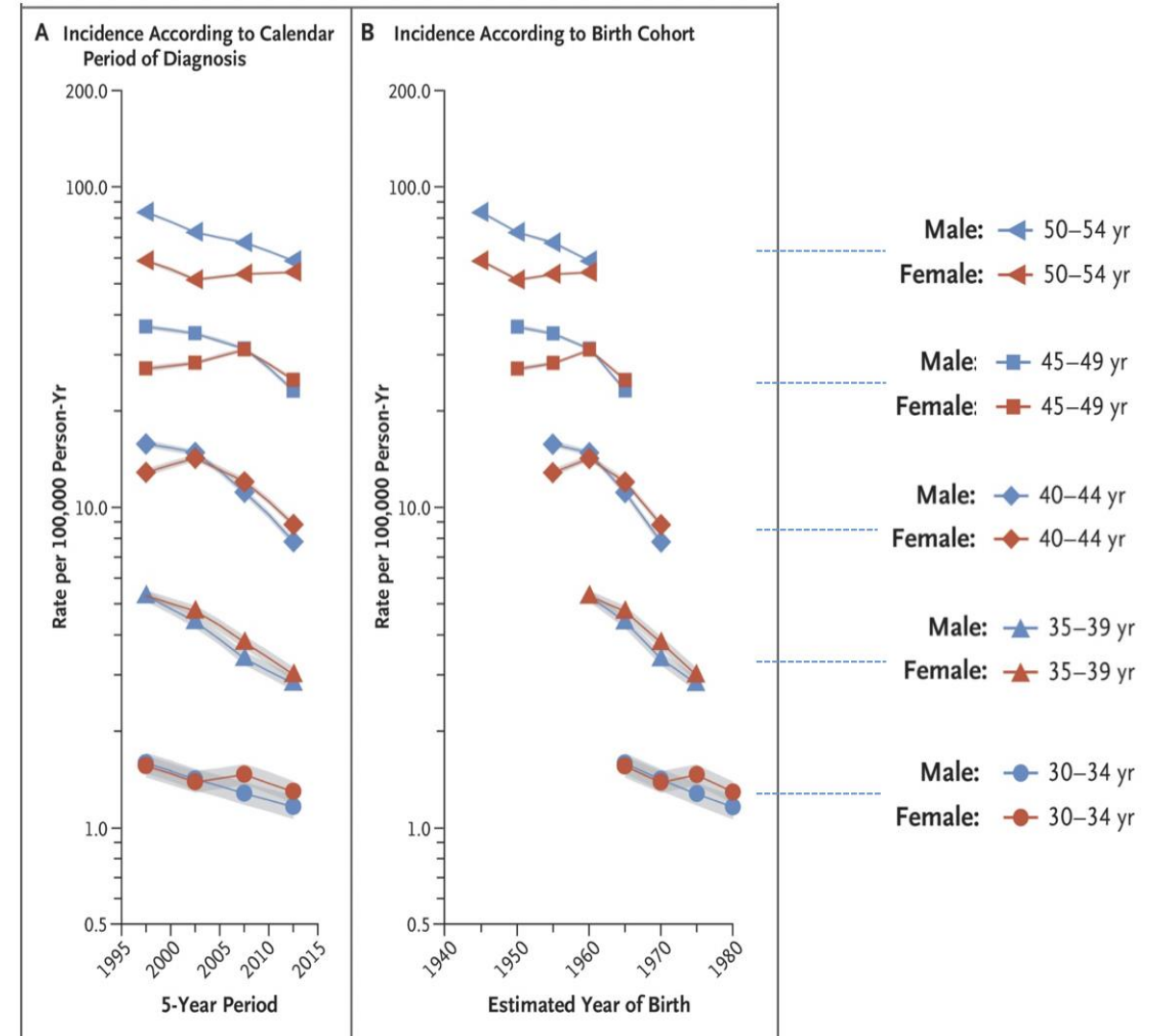
Germline findings in lung cancer:
Li-Fraumeni the main syndrome associated with lung cancer susceptibility

- Li-Fraumeni is a rare cancer susceptibility syndrome associated with germline pathogenic variants in the TP53

- The majority of Li-Fraumeni-associated lung ADC harbour EGFR somatic activating variants

- NSCLC and Li-Fraumeni syndrome *(Mezquita JTO 2020)*
  - ✓ 22 NSCLC patients, 64% women
  - ✓ Driver oncogenic alterations were observed in 90% of tumors, mainly EGFR mutated tumors

- Clinical response to a lapatinib-based therapy for a Li-Fraumeni syndrome patient with a novel HER2V659E mutation *(Serra Cancer Discov 2013)*

- Distinct NSCLC EGFR variants in a family with Li-Fraumeni syndrome: case report *(Edmonson JTO CRR 2022)*

Gender medicine and oncology: report and consensus of an ESMO workshop

A. D. Wagner[1*], S. Oertelt-Prigione[2], A. Adjei[3], T. Buclin[4], V. Cristina[1], C. Csajka[4,5], G. Coukos[1,6], U. Dafni[1,7], G.-P. Dotto[8,9,10], M. Ducreux[11], J. Fellay[12,13], J. Haanen[14], A. Hocquelet[15], I. Klinge[16], V. Lemmens[17,18], A. Letsch[19,20,21], M. Mauer[22], M. Moehler[23], S. Peters[1] & B. C. Özdemir[1,10]

Ann Oncol 2019

AGE

Host Factors
- anatomy, physiology, hormones, chromosomes
- body composition
- immune system and immune reactions
- cancer susceptibility
- preventive behaviour, exposition to risk factors

Cancer Biology
- distribution of molecular subtypes and/or gene expression profiles
- Disease presentation and evolution e.g. right-left colon cancer

Drug Effects
- pharmacokinetics, with impact on exposure, hence efficacy and toxicity
- pharmacodynamics, affecting sensitivity to beneficial and adverse effects

- Meaningful differences of both innate and adaptive immune responses between men and women explain different prevalence and mortality from autoimmune and infectious diseases
- Such sex-based differences of immune responses reflect complex interactions among genes, hormones, and environment

(Klein Nat Rev Immunol 2016, Ozdemir JCO 2018)

**Sex and gender differences may influence cancer treatment outcomes in different ways
All effects are modulated by age**

Gender medicine and oncology: report and consensus of an ESMO workshop

A. D. Wagner[1]*, S. Oertelt-Prigione[2], A. Adjei[3], T. Buclin[4], V. Cristina[1], C. Csajka[4,5], G. Coukos[1,6], U. Dafni[1,7], G.-P. Dotto[8,9,10], M. Ducreux[11], J. Fellay[12,13], J. Haanen[14], A. Hocquelet[15], I. Klinge[16], V. Lemmens[17,18], A. Letsch[19,20,21], M. Mauer[22], M. Moehler[23], S. Peters[1] & B. C. Özdemir[1,10]

Table 1. Anticancer agents with relevant differences in clearance between men and women					
Class/drug, name	Indication	*n* (men)/ (women)	Variability on CL (CV%)	Relative change in women versus men	
Angiogenesis inhibitors					
Aflibercept [47]	Advanced solid tumours	767/739	31%	Clfu Vfu	−16% −19%
Bevacizumab [48, 49]	Gastric cancer; solid tumours	1101/949	26%	CL	−14% to −27%
Antineoplastic agents: antimetabolites					
5-Fluorouracil [50, 51] and metabolite	GI malignancies; metastatic colorectal cancer	74/42	22%–40%	CL CLmet	−14% to −27% −18%
Myeloablative agents					
Busulfan [52]	Marrow transplantation	904/689	22%	V	+7%
Antineoplastic agent: alkylating agents					
Temozolomide [53, 54]	Glioma, glioblastoma, melanoma	303/177	5%–10%	CL	−19 to 27%
Mephalan [55]	Advanced malignancies	22/42	45%	CL	−19%
Trabectedin [56]	PD study	232/467	51%	V Keo	−17% +22%
Antineoplastic agents: alkaloids					
Paclitaxel [57, 58]	Solid tumours	159/160		CL Vmax	−30% +14%
Irinotecan (SN38) [59–61]	Solid tumours, glioblastoma	67/58	47%	CL	−30% to 38%
Antineoplastic agent: antibodies					
Rituximab [62]	Lymphoma	16/13	19%	CL	−21%

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

Immune checkpoint inhibitors improve OS for patients with advanced cancers such as melanoma and NSCLC, but the magnitude of benefit is sex-dependent

	Line of treatment	Intervention (number of patients)	Control (number of patients)		HR (95% CI)
Melanoma					
Hodi et al (2010)[36]	>1	Ipilimumab (n=137)	gp100 (n=136)		0·81 (0·55–1·20)
					0·54 (0·37–0·77)
		Ipilimumab plus gp100 (n=403)	gp100 (n=136)		0·72 (0·52–0·99)
					0·66 (0·50–0·87)
Robert et al (2011)[35]	1	Ipilimumab plus dacarbazine (n=250)	Dacarbazine plus placebo (n=252)		0·86 (0·63–1·17)
					0·70 (0·55–0·90)
Ribas et al (2013)[41]	1	Tremelimumab (n=328)	ICC (n=327)		0·81 (0·62–1·06)
					0·93 (0·74–1·17)
Robert et al (2015)[39]	1	Nivolumab (n=210)	Dacarbazine (n=208)		0·56 (0·33–0·95)
					0·34 (0·22–0·54)
Robert et al (2015)[37]	>1	Pembrolizumab q2w (n=279)	Ipilimumab (n=278)		0·69 (0·46–1·04)
					0·57 (0·39–0·84)
		Pembrolizumab q3w (n=277)	Ipilimumab (n=278)		0·78 (0·50–1·21)
					0·66 (0·46–0·95)
Hodi et al (2016)[38]	1	Nivolumab plus Ipilimumab (n=95)	Ipilimumab plus placebo (n=47)		0·89 (0·36–2·19)
					0·65 (0·33–1·26)
Larkin et al (2018)[40]	>1	Nivolumab (n=272)	ICC (n=133)		1·07 (0·69–1·65)
					0·85 (0·62–1·17)
Non-small-cell lung cancer					
Borghaei et al (2015)[49]	>1	Nivolumab (n=292)	Docetaxel (n=290)		0·78 (0·58–1·04)
					0·73 (0·56–0·96)
Brahmer et al (2015)[47]	>1	Nivolumab (n=135)	Docetaxel (n=137)		0·67 (0·36–1·25)
					0·57 (0·41–0·78)
Herbst et al (2016)[45]	>1	Pembrolizumab (n=690)	Docetaxel (n=343)		0·69 (0·51–0·94)
					0·65 (0·52–0·81)
Reck et al (2016)[44]	1	Pembrolizumab (n=154)	ICC (n=151)		0·96 (0·56–1·64)
					0·54 (0·36–0·80)
Carbone et al (2017)[43]	1	Nivolumab (n=271)	ICC (n=270)		1·15 (0·79–1·66)
					0·97 (0·74–1·26)
Govindan et al (2017)[48]	1	Ipilimumab plus paclitaxel plus carboplatin (n=388)	Paclitaxel plus carboplatin plus placebo (n=361)		1·33 (0·84–2·11)
					0·85 (0·71–1·02)
Small-cell lung cancer					
Reck et al (2016)[42]	1	Ipilimumab plus etoposide plus platinum (n=478)	Etoposide plus platinum plus placebo (n=476)		1·06 (0·81–1·37)
					1·07 (0·89–1·28)
Mesothelioma					
Maio et al (2017)[50]	>1	Tremelimumab (n=382)	Placebo (n=189)		1·12 (0·72–1·75)
Head and neck cancer					0·91 (0·73–1·13)
Ferris et al (2016)[53]	>1	Nivolumab (n=240)	ICC (n=121)		0·93 (0·47–1·85)
					0·65 (0·48–0·88)
Cohen et al (2017)[54]	>1	Pembrolizumab (n=247)	ICC (n=248)		1·03 (0·61–1·72)
Renal cell carcinoma					0·73 (0·61–0·92)
Motzer et al (2015)[51]	>1	Nivolumab (n=410)	Everolimus (n=411)		0·84 (0·57–1·24)
Stomach cancer					0·73 (0·58–0·92)
Kang et al (2017)[55]	>1	Nivolumab (n=330)	Placebo (n=163)		0·83 (0·56–1·23)
Urothelial cancer					0·59 (0·46–0·75)
Bellmunt et al (2017)[52]	>1	Pembrolizumab (n=270)	ICC (n=272)		0·78 (0·49–1·24)
					0·73 (0·56–0·94)
Pooled estimate in women					**0·86 (0·79–0·93)**
Pooled estimate in men					**0·72 (0·65–0·79)**

p_heterogeneity=0·0019

Women
Men

0·25   0·5   1·0   2·0   4·0
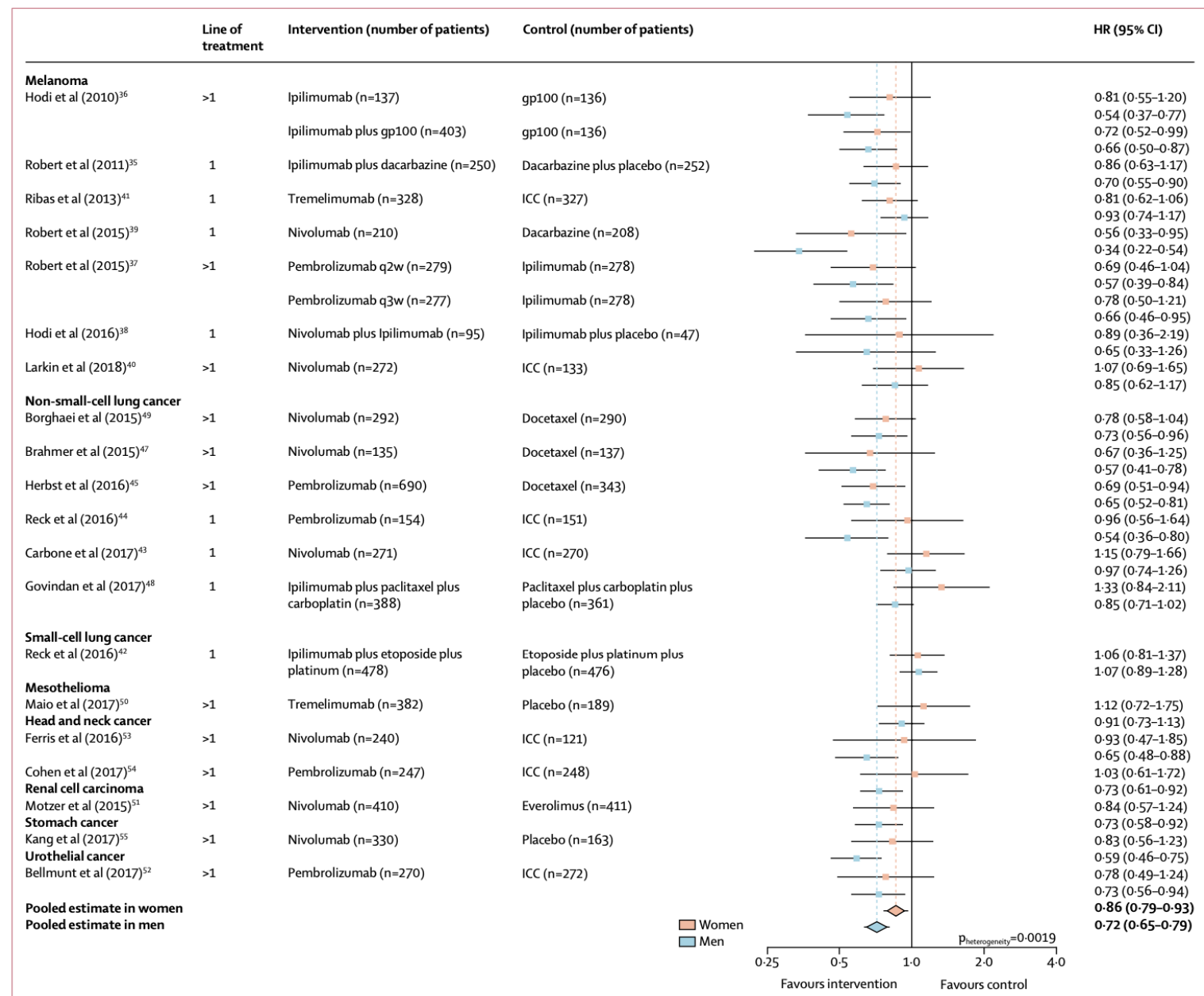
Favours intervention   Favours control

Figure 2: Hazard ratios of death for patients assigned to intervention treatment, compared with those assigned to control treatment, by sex
Squares represent study-specific HRs. Horizontal lines indicate the 95% CIs. Diamonds indicate the meta-analytic pooled HRs, calculated separately in females and males, with their corresponding 95% CIs. The dashed vertical lines indicate the gender-specific pooled HRs. The p value for heterogeneity is from the meta-analysis of the interaction HRs and represents heterogeneity by patients' sex. gp100=glycoprotein 100. HR=hazard ratio. ICC=investigator's choice chemotherapy. q2w=every 2 weeks. q3w=every 3 weeks.

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, Filippo De Marinis, Richard D. Gelber, Aron Goldhirsch
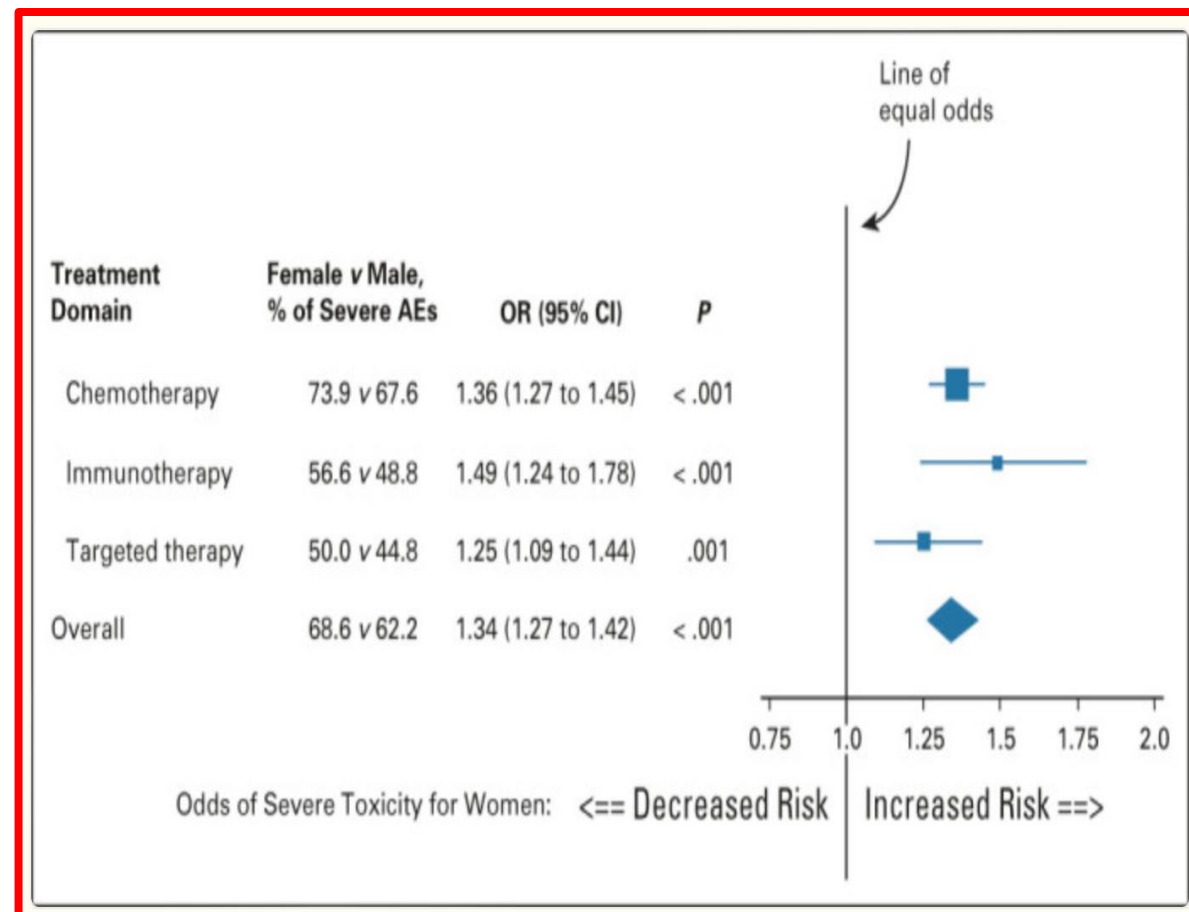
- **A greater effect of anti–PD1 alone in men**
- **A greater effect for anti–PD1/ PDL1 plus CT in women**
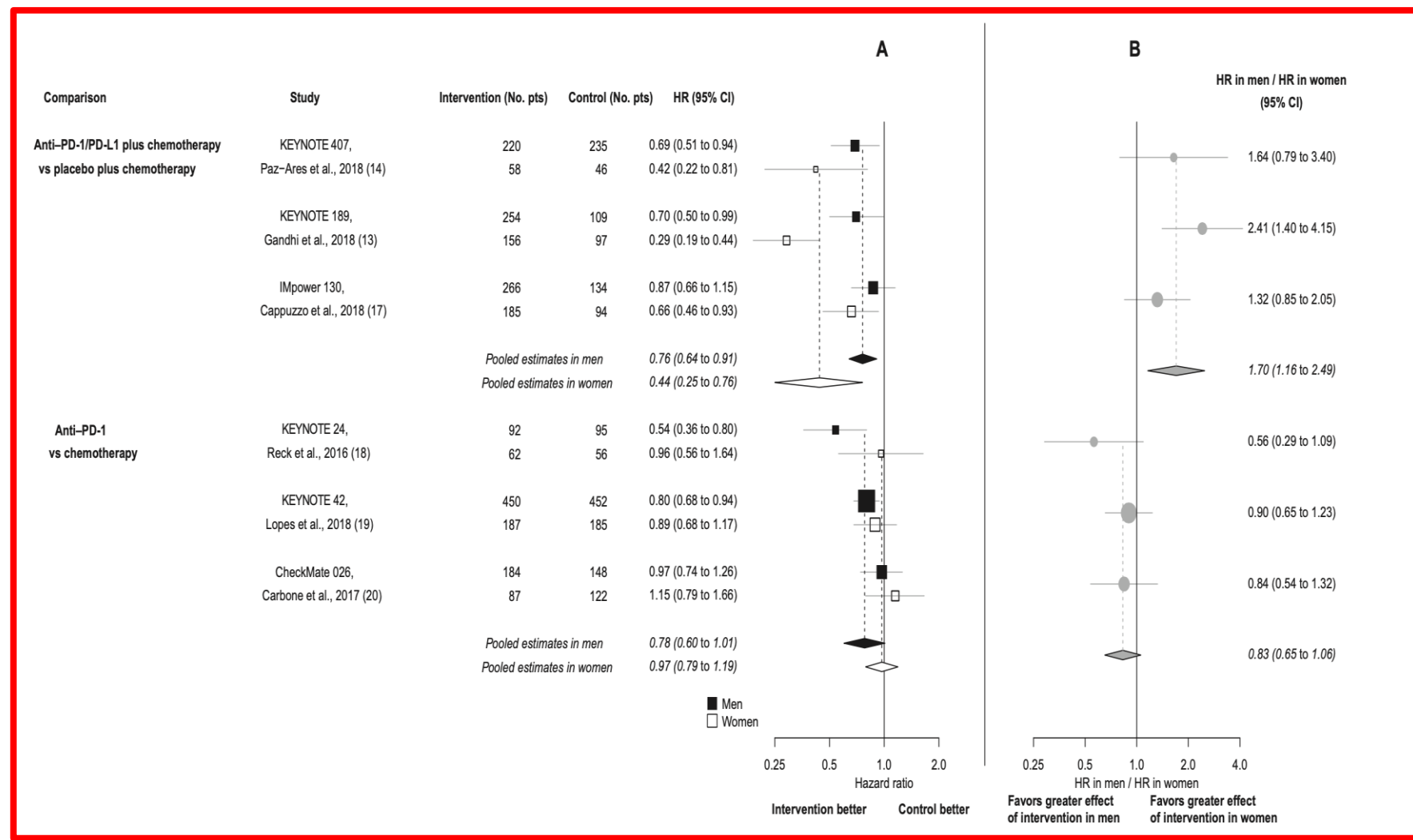
HRs of death according to sex and type of immunotherapeutic strategy

Sex differences in risk of severe AEs in patients receiving immunotherapy, targeted therapy, or CT in cancer clinical trials *(Unger JCO 2022)*

- In total, 23,296 patients (women, 37.9%; men, 62.1%) from 202 trials were analyzed

- Overall, 64.6% experienced one or more severe (G $\geq$3) AEs

- Women had a 34% increased risk of severe AEs compared with men (OR 1.34; P , .001), including a 49% increased risk among those receiving ICI (OR 1.49; P , .001)

- Women experienced an increased risk of severe symptomatic AEs among all treatments, especially ICI (OR 1.66; 95% CI, 1.37 to 2.01; P , .001)

- Women receiving CT experienced increased severe hematologic AE

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

Odds of Severe Toxicity for Women: <== Decreased Risk | Increased Risk ==>

CT lung cancer screening: findings from the NELSON trial

- NELSON, the second largest randomized controlled trial to demonstrate a reduction in lung cancer mortality with CT screening of people at high risk

- Overall, CT scanning decreased mortality by 24% in high-risk men and 33% in high-risk women over a 10-year period

Lung cancer mortality rate ratio (95% CI)	Year 8	Year 9	Year 10
MALES	0.75 P=0.015 (0.59–0.95)	0.76 P=0.012 (0.60–0.95)	0.74 P=0.003 (0.60–0.91)
FEMALES	0.39 P=0.0037 (0.18–0.78)	0.47 P=0.0069 (0.25–0.84)	0.61 P=0.0543 (0.35–1.04)

Women represents only 16% of population

Rand: 23-12-2003 – 06-07-2006

FU: 23-12-2003 – 31-12-2015

FU 94% complete year 10

WCLC 2018

Harry J. de Koning, Erasmus MC, Public Health Rotterdam

de Koning WCLC 2018, NEJM 2020

Take home messages

- Lung cancer is the second leading cause of cancer-related deaths among women worldwide

- Lung cancer cases by smoking are preventable

- Two-thirds of lung cancer never smoker are women

- EGFRm more frequent in never females *vs* males

- Sex differences in the immune system and immune reactions

- Future opportunities to reduce cancer mortality through improvements in screening and early detection

Gràcies!!!
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