Relationship of Lung Cancer and Emphysema

Lung Cancer Workshop X

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Are they related? If so, why/how?

- Common things are common.

- Shared risk factors.

- Shared genetic predisposition.

- Shared mechanisms.

He's one of the busiest men in town. While his door may say *Office Hours 2 to 4*, he's actually on call 24 hours a day.

The doctor is a scientist, a diplomat, and a friendly sympathetic human being all in one, no matter how long and hard his schedule.

According to a recent Nationwide survey:

MORE DOCTORS SMOKE CAMELS THAN ANY OTHER CIGARETTE

DOCTORS in every branch of medicine—113,597 in all—were queried in this nationwide study of cigarette preference. Three leading research organizations made the survey. The gist of the query was—What cigarette do you smoke, Doctor?

The brand named most was Camel!

The rich, full flavor and cool mildness of Camel's superb blend of costlier tobaccos seem to have the same appeal to the smoking tastes of doctors as to millions of other smokers. If you are a Camel smoker, this preference among doctors will hardly surprise you. If you're not—well, try Camels now.

Your "T-Zone" Will Tell You...

T for Taste...
T for Throat...

that's your proving ground for any cigarette. See if Camels don't suit your "T-Zone" to a "T."

CAMELS *Costlier Tobaccos*

To celebrate her latest creation, assistant milliner Lisa Walsh lit up a cigarette right in the shop.

Unfortunately, she soon found herself working for a mad hatter.

VIRGINIA SLIMS
You've come a long way, baby.

© Philip Morris Inc. 1989

9 mg "tar," 0.7 mg nicotine av. per cigarette by FTC method.

**SURGEON GENERAL'S WARNING:** Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.

Found in Mom's Basement

Significance of the Problem:

- COPD and lung cancer are highly prevalent and conditions with associated morbidity and mortality.

- The most significant risk factor for both COPD and lung cancer in the developed world is cigarette smoking.[1]

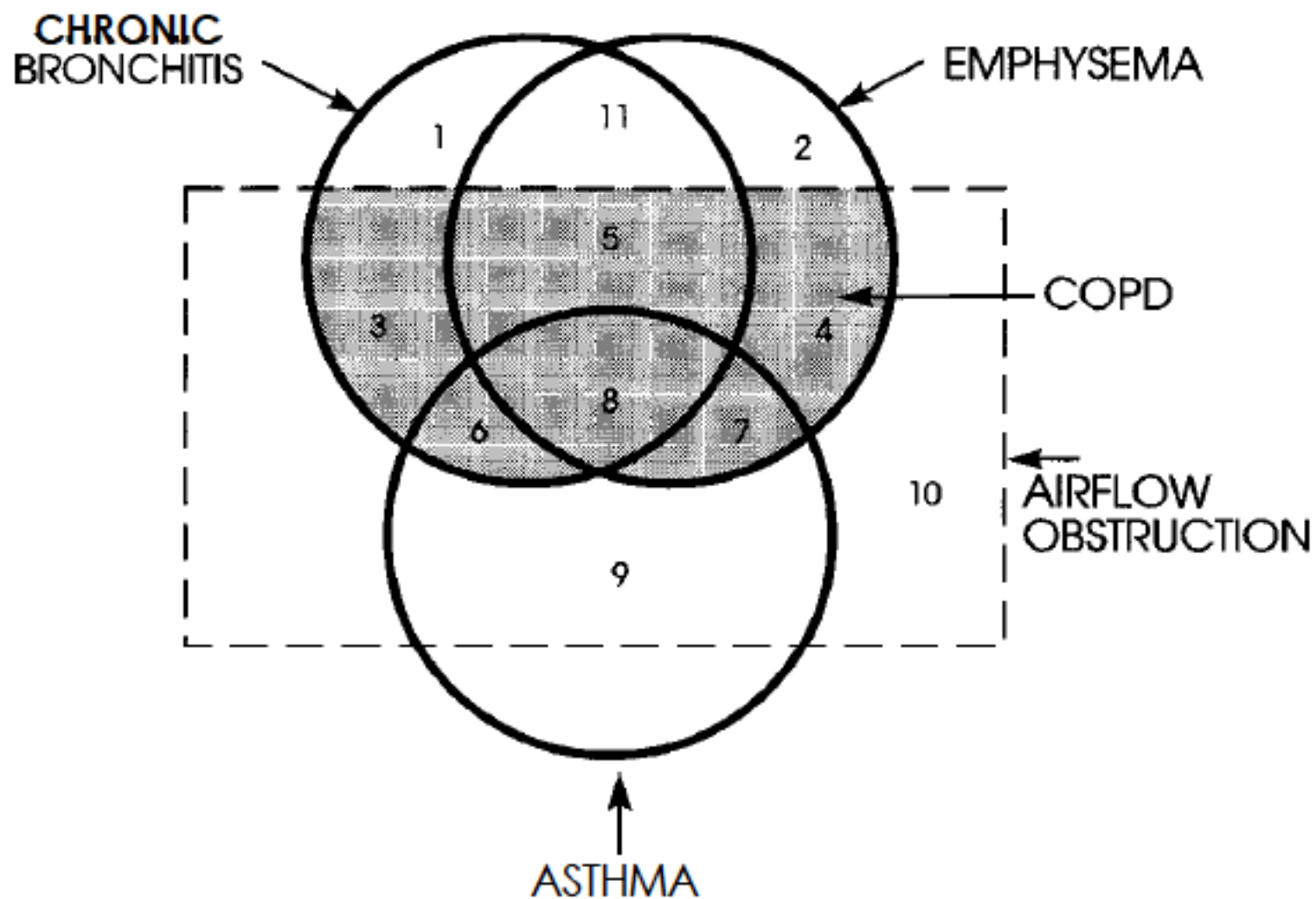- An estimated 100 million Americans are current or former smokers.[2]
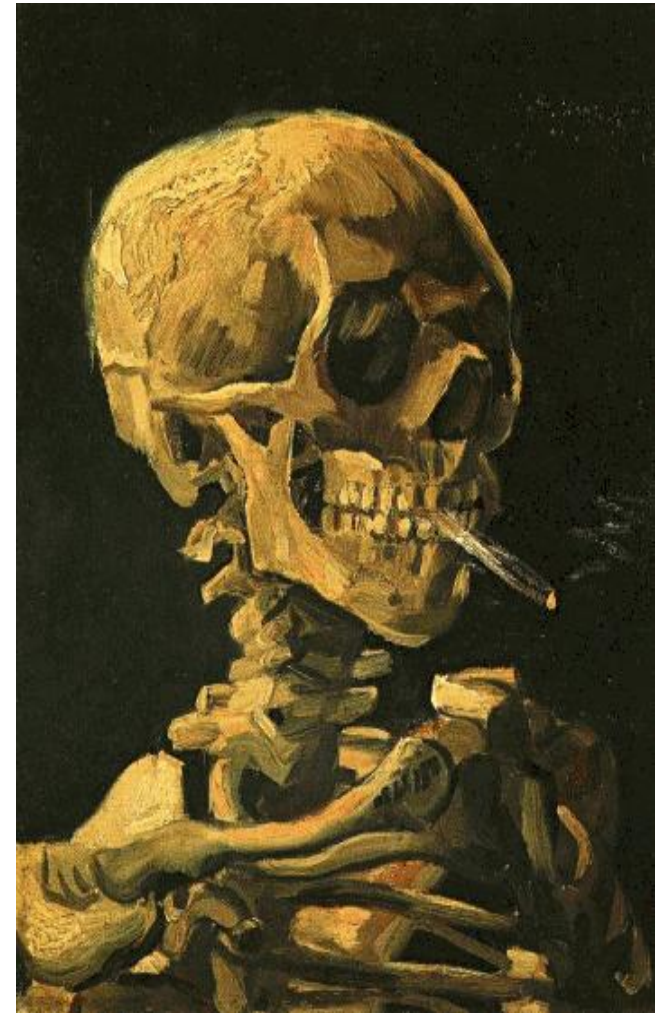
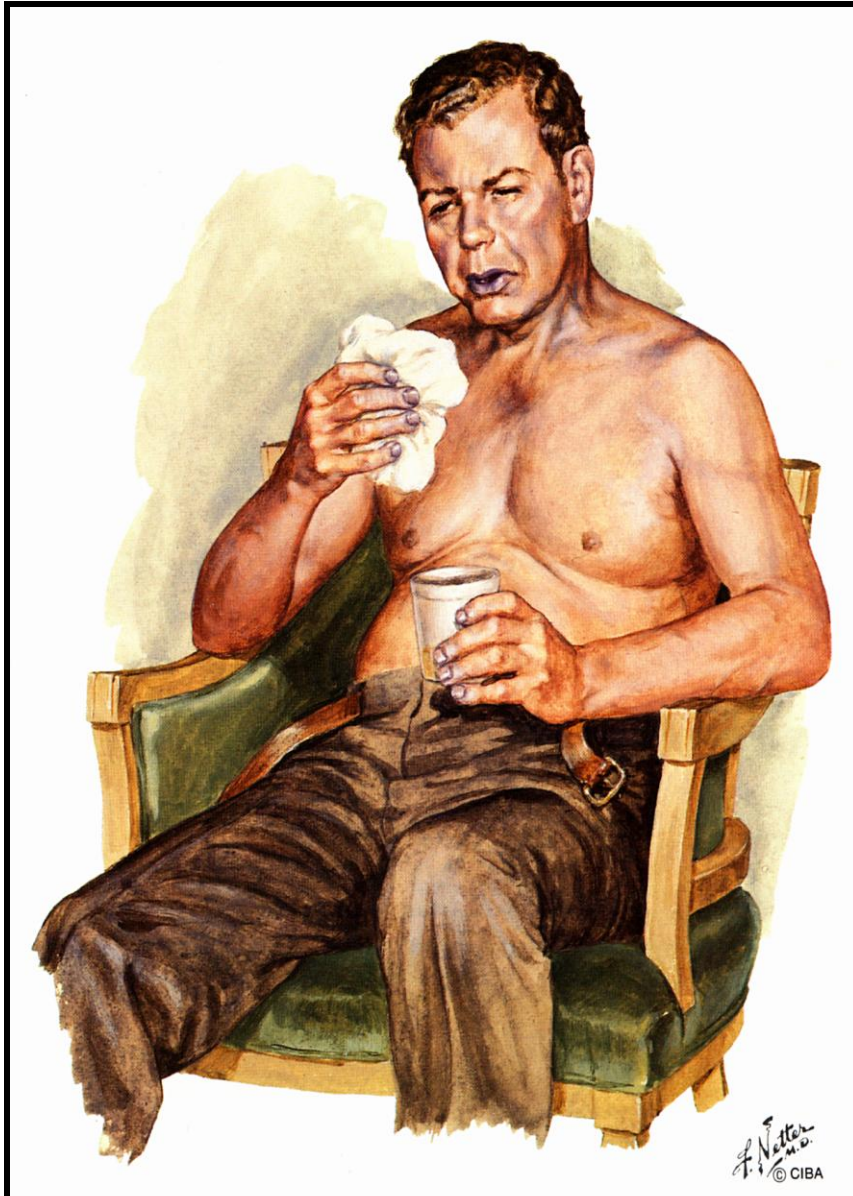1. .Mannino et al. Proc Am Thorac Soc 2007.   2. Mahadevia et al. JAMA 2003.
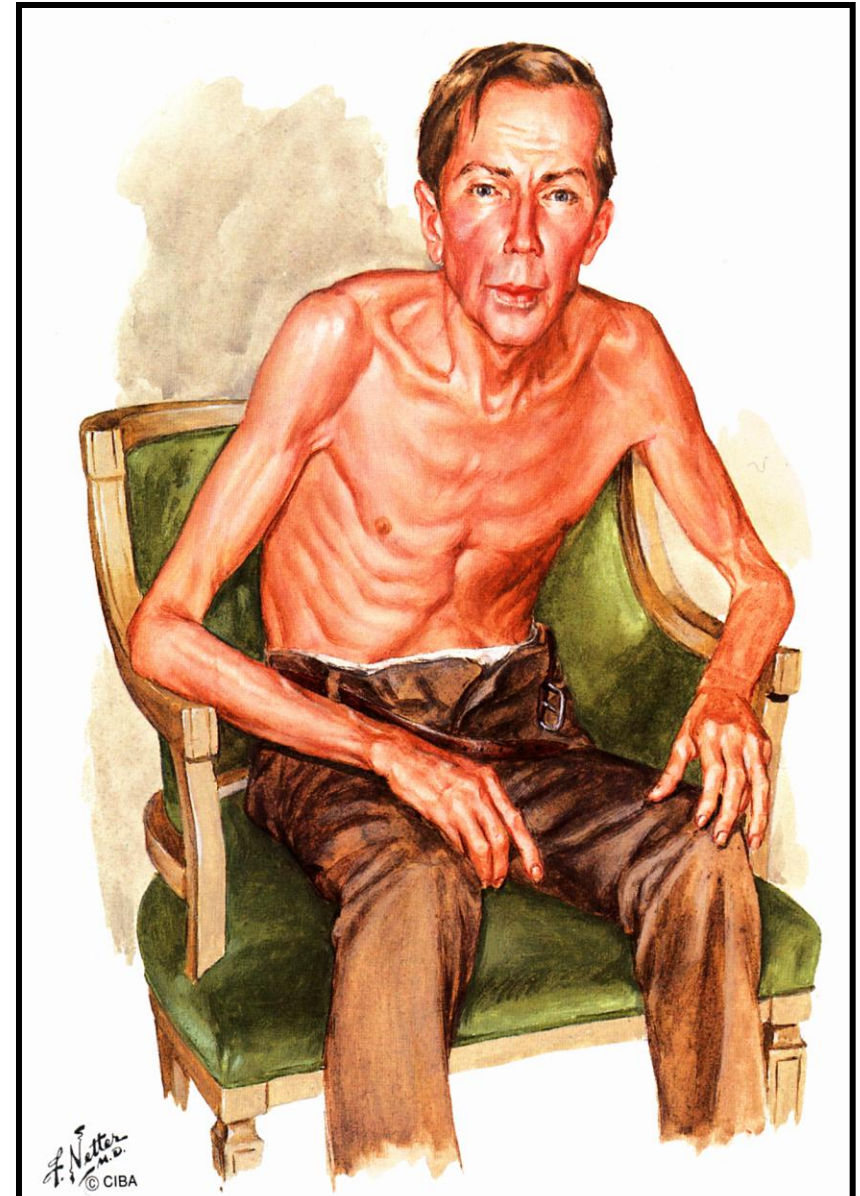
U.S. Deaths From COPD
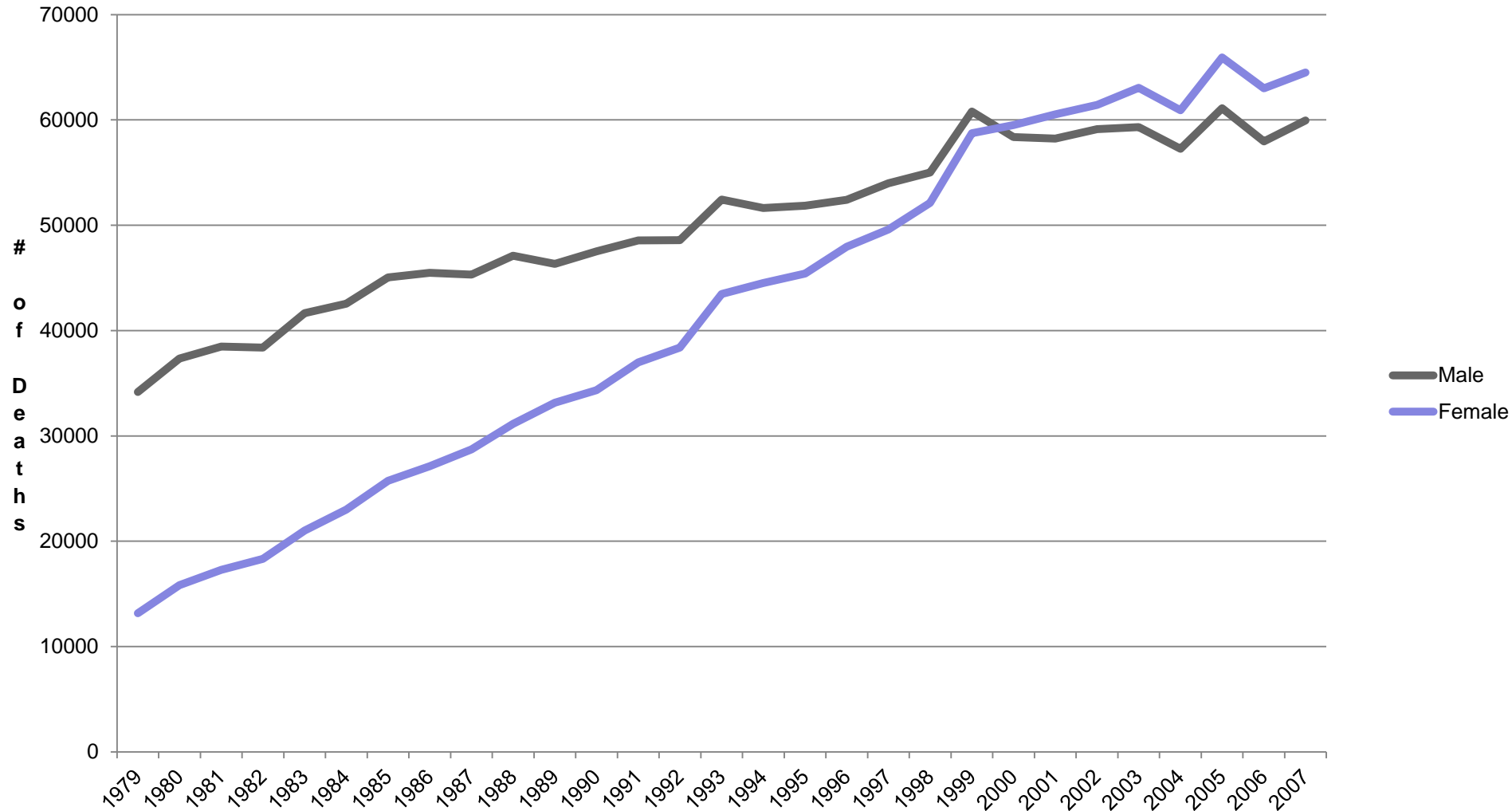
Data from American Lung Association 2011 Report: Trends in Chronic Bronchitis and Emphysema Morbidity and Mortality
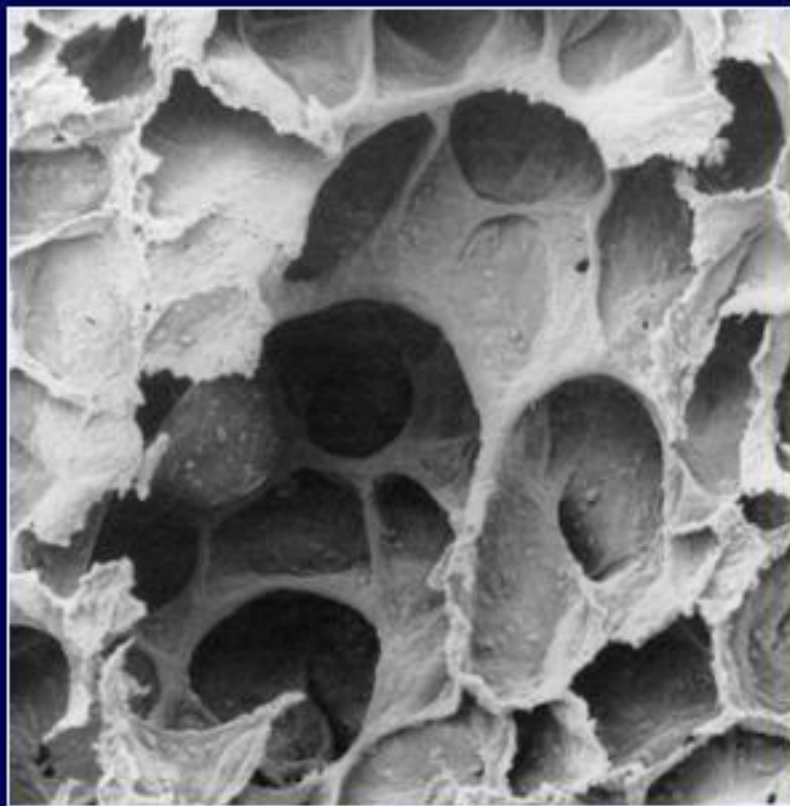
"Blue Bloater"   "Pink Puffer"

Alveolar Destruction With Emphysema

Normal

Emphysema

FEV$_1$ 105%
DlCO 50%

FEV$_1$ 95%

DlCO 70%
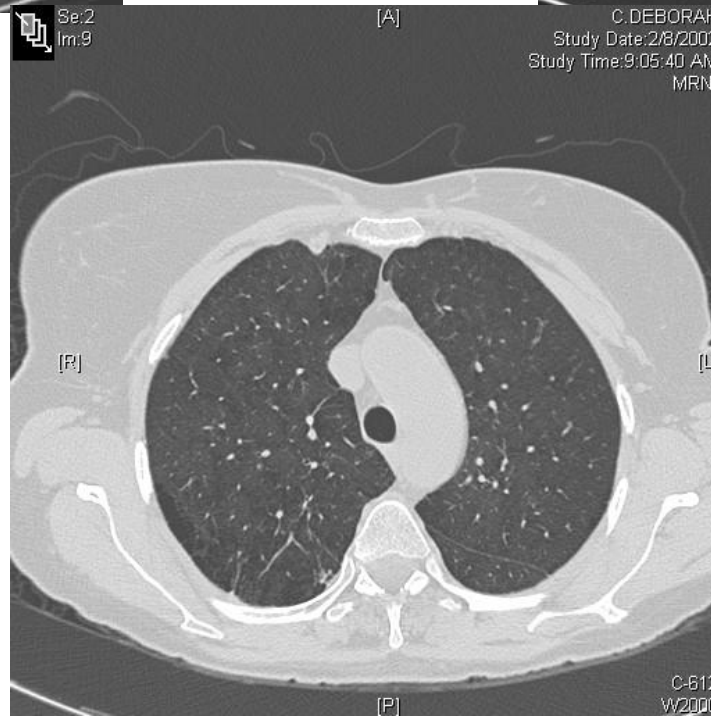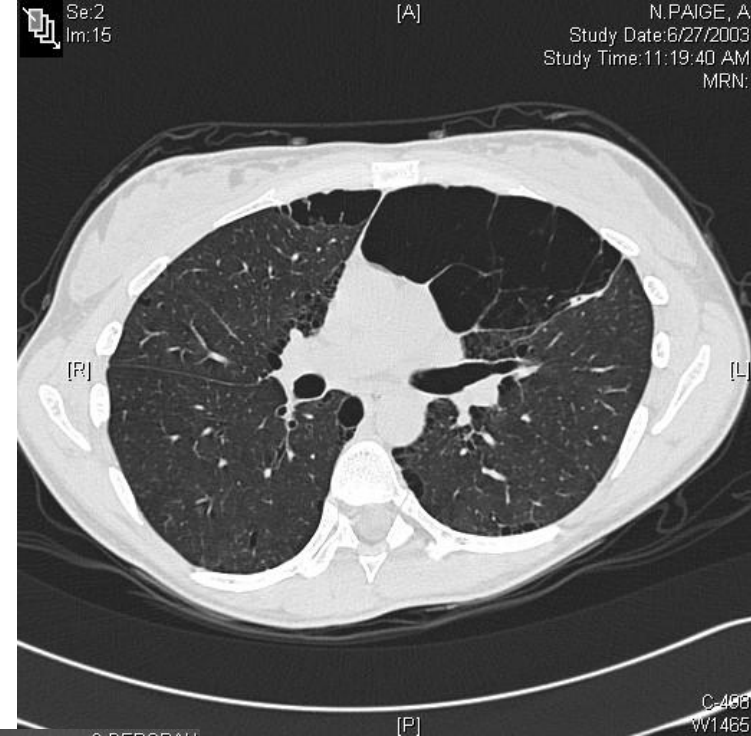
FEV$_1$ 40%
DlCO 70%

Relationship of CT Density Mask Quantification of Emphysema and % Predicted FEV1

R = -0.19

% emphysema (-910 HU) vs FEV1 % Predicted
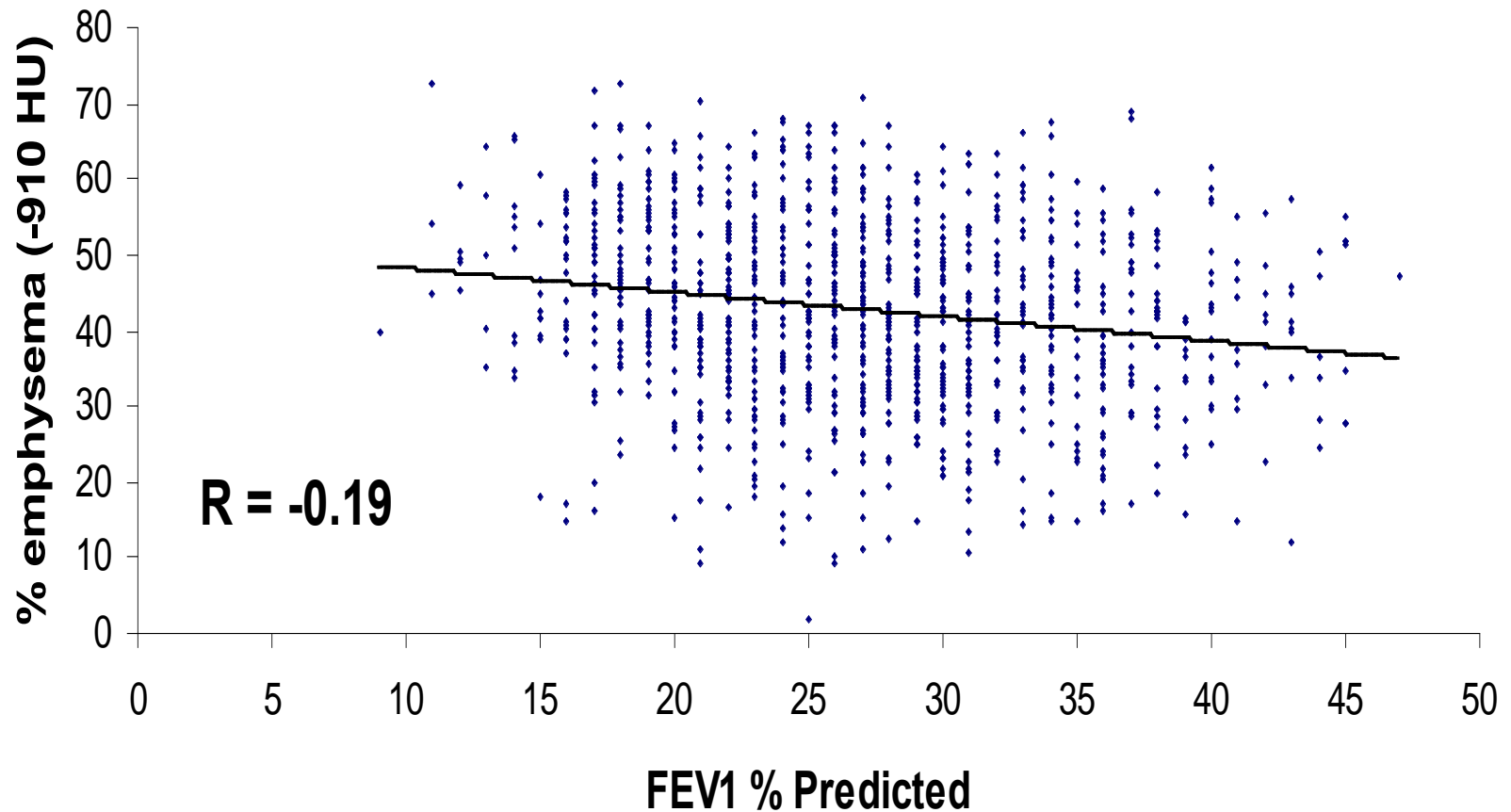
Measuring Emphysema on CT scan: Man vs. Machine

- ## Man:
  - Predictive of response to surgery
  - Somewhat reproducible
  - Not always a scalable solution: slow

- ## Machine:
  - Highly reproducible
  - Very fast
  - Does not recognize 'patterns' as well as trained human

Relationship of Lung Cancer and COPD:

- Lung cancer risk has been associated with airflow obstruction.[1-4]

- Lung cancer risk has been associated with presence of emphysema on CT scan.[5,6]

Airflow obstruction	Radiographic emphysema	Lung cancer Yes	Lung cancer No
III-IV	Yes	15	154
III-IV	No	0	63
II	Yes	32	472
II	No	4	320
I	Yes	11	287
I	No	5	190
None	Yes	17	558
None	No	15	1,495

Odds ratio
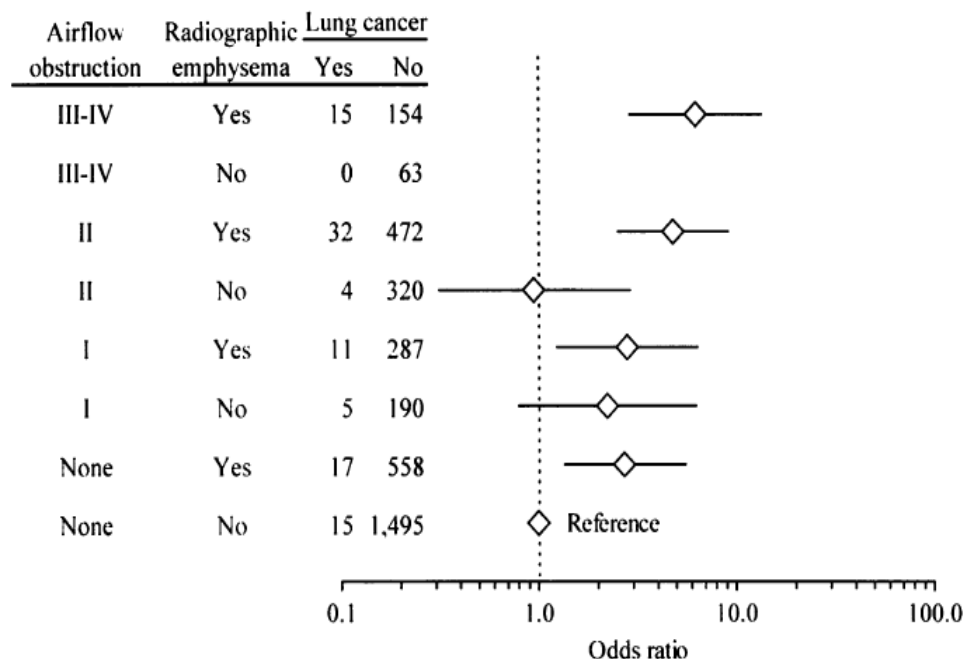
1. Skillrud et al. Ann Int Med 1986.
2. Mannino et al. Arch Int Med 2003.
3. Tockman Ann Intern Med 1987.
4. Wasswa-Kintu et al. Thorax 2007.
5. de Torres et al. Chest 2007.
6. Wilson et al. AJRCCM 2008.

Study	Number of participants	Outcome	FEV$_1$ (% predicted)[‡]	Emphysema
Skilrud et al.[4]	226	Incidence	Cancers in 8.8% of cases (FEV$_1$ <70%) versus 2.0% of controls (FEV$_1$ >85%); $P=0.024$	NA
Tockman et al.[5]	4,395	Mortality	• Cohort 1: RR 4.85 for FEV$_1$ <60% versus >60%; $P=0.002$ • Cohort 2: RR 2.72 for FEV$_1$ 60–85% versus >85%; $P=0.043$	NA
Speizer et al.[7]	8,427	Mortality	Quartile-based FEV$_1$ analysis confers cancer risk (RR 2.0–8.27)	NA
Lange et al.[6]	13,946	Mortality	• RR 2.1 (95% CI 1.3–3.4) for FEV$_1$ 40–79% versus >80% • RR 3.9 (95% CI 2.2–7.2) for FEV$_1$ <40% versus >80%	NA
de Torres et al.[19]	1,166	Incidence	RR 2.89 (95% CI 1.14–7.27) for FEV$_1$/FVC ratio <70% versus >70%	Semi-quantitative radiographic emphysema, RR 3.13 (95% CI 1.32–7.44)
Wilson et al.[17]	3,638	Incidence	OR 2.09 (95% CI 1.33–3.27) for any GOLD stage (FEV$_1$/FVC <70%)	Semi-quantitative radiographic emphysema, OR 3.56 (95% CI 2.21–5.73). After controlling for airflow obstruction, OR 3.14 (95% CI 1.91–5.15) for radiographic emphysema
Li et al.[20]	1,015	Incidence	NA	Semi-quantitative radiographic emphysema. Any = OR 2.79 (95% CI 2.05–3.81), >5% = 3.80 (95% CI 2.78–5.19), >10% = OR 3.33 (95% CI 2.30–4.82)
Zulueta et al.[21]	9,047	Mortality	NA	Semi-quantitative radiographic emphysema, HR 1.7 (95% CI 1.1–2.5); $P=0.013$
Maldanado et al.[23]	1,520	Incidence	Cancer risk conferred by decreasing FEV$_1$, OR 1.15 (95% CI 1.00–1.32; $P=0.046$); and FEV$_1$/FVC <70%, OR 1.29 (95% CI 1.02–1.62; $P=0.0310$)	Automated volumetric determination of radiographic emphysema was not associated with lung cancer risk, OR 1.042 (95% CI, 0.816–1.329; $P=0.743$)

CI, confidence interval; FEV$_1$, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global Initiative for Chronic Obstructive Lung Disease; HR, hazard ratio; NA, not applicable; OR, odds ratio; RR, relative risk. *All studies controlled for age and cigarette consumption. ‡The FEV$_1$ is reported as the percentage that would be predicted for that individual based on parameters that are known to influence the FEV$_1$, such as gender, age, height and race.

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Gene	COPD	Lung cancer
SERPINA1	MZ heterozygotes associated with COPD (P=0.04)[151]	A1AT carrier rate (12.3%) exceeded expected control rate (P=0.002)[152]
MMP1	Combined MMP1 and MMP12 SNPs associated with rapid decline in lung function[115]	MMP1 promoter SNP associated with lung cancer risk (OR 1.8; 95% CI 1.3–2.4)[153]
CYP1A1	Homozygous *2A allele significantly higher in severe COPD (P<0.01)[154]	M1 homozygous genotype found in 4.10% cancers versus 1.69% controls[155]
EPHX1	Increased COPD risk for exon 3 variant both as heterozygote (OR 3.0; 95% CI 1.2–7.1) and homozygote (OR 2.4; 95% CI 1.1–5.1)[156,157]	Lung cancer risk associated with high EPHX activity (P<0.02)[158]
CHRNA3 and CHRNA5	CHRNA3 and CHRNA5 locus significantly associated with both radiographic emphysema (P<0.0002) and airflow obstruction (P=0.004)[38]	CHRNA3 and CHRNA5 locus strongly associated with lung cancer in three independent studies[40]
MPO	NA	Reduced risk (OR 0.5; 95% CI, 0.29–0.88) of lung cancer with A/G allele (reduced expression)[93]

CHRNA3, cholinergic receptor, neuronal nicotinic, α-polypeptide 3; CI, confidence interval; COPD, chronic obstructive pulmonary disease; CYP1A1, cytochrome P450 subfamily 1, polypeptide 1; EPHX1, epoxide hydrolase 1; MMP, matrix metalloproteinase; MPO, myeloperoxidase; MZ, individuals that have one normal allele of SERPINA1 and a commonly encountered abnormal allele designated Z; NA, not applicable; OR, odds ratio; SNP, single nucelotide polymorphism.

Potential Common Mechanisms:

1.   Houghton et al. Nat Med 2008.
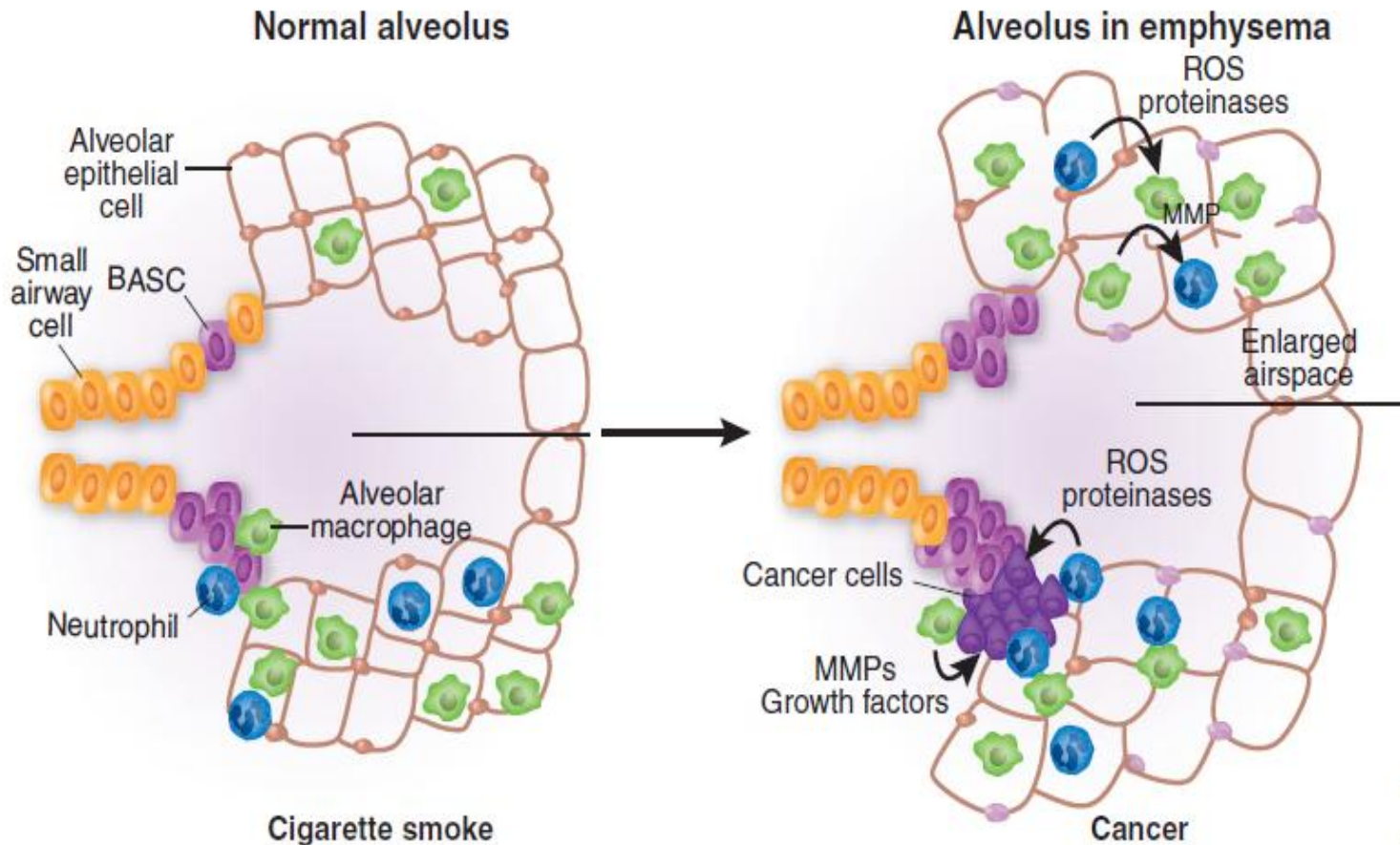
Proteinase	Source	Matrix substrates	Promotes emphysema?	Promotes cancer?	Refs
Neutrophil elastase	PMNs	Elastin, CI, CIII, CIV, laminin, fibronectin and TIMPs	Yes	Yes	122,123
Proteinase 3	PMNs	Elastin, CIV, laminin and fibronectin	Yes	?	159
Cathepsin S	Macrophages and other cell types	Elastin, CI, CIII, laminin and fibronectin	Yes	Yes	160,161
Cathepsin L	Macrophages and other cell types	Elastin, CI, CIII, laminin and fibronectin	?	Yes	162
Cathepsin K	Macrophages and other cell types	Elastin, CI, CIII, laminin and fibronectin	?	?	163
MMP1	Stromal cells	CI, CIII and A1AT	Yes	Yes	112,114
MMP2	Stromal cells	Elastin, CI, CIV, laminin, fibronectin and A1AT	?	Yes	164
MMP3	Stromal cells	Elastin, CIII, CIV, laminin, fibronectin and A1AT	No	Yes	165
MMP8	PMNs	CI, CIII and A1AT	No	No	166
MMP9	Macrophages, PMN and other cell types	Elastin, CI, CIV, laminin and A1AT	Yes	Yes	106,107, 109
MMP12	Macrophages	Elastin, CI, CIV, fibronectin, laminin and A1AT	Yes	No	116,119
MMP13	Stromal cells	CI, CIII and CIV	No	Yes	167
MMP14	Stromal cells and macrophages	CI, CIII, CIV, fibronectin and laminin	?	Yes	168,169

CI, collagen type I; CIII, collagen type III; CIV, collagen type IV; MMP, matrix metalloproteinase; PMNs, polymorphonuclear leukocytes; TIMP, tissue inhibitors of metalloproteinase.

COPD

COPD with cancer

?

Tumour

Genetics:
- Process oxidant or noxious stress
- EPHX, CYPs, MPO and NRF2

Cell cycle regulation:
- Avoid apoptosis
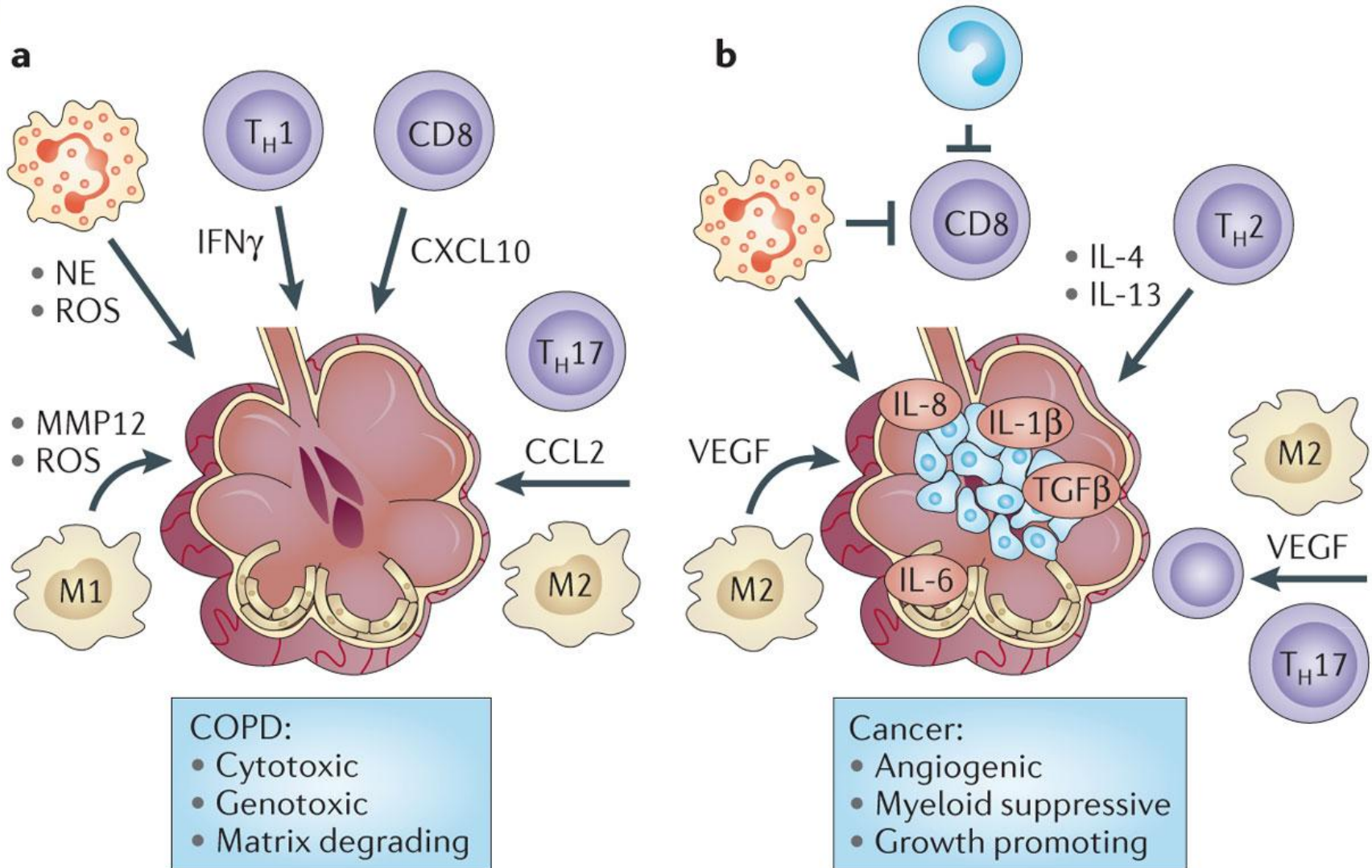- Uncontrolled proliferation

Cytokines:
- NF-κB activation
- Regulate tumour microenvironment

Inflammation:
- Field propagation
- Cytotoxic versus growth promoting

Proteinases:
- Matrix degradation
- Release growth factors

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Conclusions:

- Weight of evidence supports a greater than chance association of emphysema and lung cancer.

- There are plausible mechanistic hypotheses for this association.

- Changes in lung structure imaged on CT scanning are a marker for increased risk.