

Cancer, hypertension et antihypertenseurs

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Le cancer: cause no 1 des décès chez les hommes
Santé Pour la première fois en 2016 plus d'hommes sont décédés à cause de cancers que par des maladies cardio-vasculaires.

Outline of the presentation

- 1) Is hypertension a risk factor for cancer per se ?
- 2) Is there an increased risk of cancer with antihypertensive drugs?
- 3) Diuretics and risk of cancer
- 4) Diuretic and risk of skin cancer
- 5) What are the actual trends in cancer and cardiovascular mortalities

HIGH BLOOD-PRESSURE: A RISK FACTOR FOR CANCER MORTALITY?

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**TABLE II—1958 SYSTOLIC AND DIASTOLIC BLOOD-PRESSURE AND
FOURTEEN-YEAR MORTALITY RATES PER 1000 IN 1233 WHITE
MALES AGE 40–59 IN 1958: CHICAGO PEOPLES GAS COMPANY
STUDY, 1958–72**

Variable	Blood- pressure	No.	Total death		C.V.R. death		Cancer death		
			No.	Rate	No.	Rate	No.	Crude rate	Net rate
Systolic blood- pressure	≤ 119	258	40	186	19	90	11	52	64
	120–127	256	34	146	17	70	9	39	45
	128–135	220	33	147	12	54	13	57	64
	136–147	245	50	196	31	127	12	45	55
	≥ 148	254	89	301	46	147	26	98	128
Diastolic blood- pressure	< 140	817	119	156	59	77	34	45	52
	≥ 140	416	127	273	66	143	37	82	105
	< 160	1098	190	177	95	88	53	50	59
	≥ 160	135	56	361	30	175	18	136	180
	< 70	210	31	165	16	88	7	36	45
	71–79	238	36	156	16	67	11	49	56
	80	250	49	192	24	93	17	67	77
	81–89	278	48	164	26	92	15	50	59
	≥ 90	257	82	294	43	153	21	78	106
	< 90	976	164	171	82	85	50	53	61
	≥ 90	257	82	294	43	153	21	78	106
	< 95	1118	205	186	102	92	60	55	66
	≥ 95	115	41	341	23	184	11	104	135

Seventeen-year cancer mortality: Western Electric Health Study
(5397 men aged 40–55 years)

	No. at risk	Cancer deaths [n (%)]	RR
Baseline SBP (mmHg)			
87–125	705	20 (2.84)	1.00
126–139	655	26 (3.97)	1.40
140–247	683	37 (5.42)	1.90

Incidence of cancer at specific sites during 20 years' follow-up by fifths of systolic BP distribution, per 10 000 person-years in Sweden

Site	SBP (mmHg)					Total (7396)	Age-adjusted relative risk (95% confidence interval) for SBP > 166/< 130 mmHg
	< 130 (1593)	130–140 (1390)	141–152 (1648)	153–166 (1365)	> 166 (1400)		
Oropharyngeal	5 (15)	2 (6)	4 (13)	3 (7)	5 (12)	4 (53)	1.03 (0.48–2.21)
Stomach	4 (13)	4 (10)	2 (6)	5 (13)	6 (14)	4 (56)	1.28 (0.60–2.73)
Colon and rectum	9 (27)	11 (28)	10 (30)	13 (32)	14 (33)	11 (150)	1.46 (0.88–2.44)
Liver	3 (9)	2 (6)	3 (9)	2 (6)	2 (5)	3 (35)	0.71 (0.24–2.13)
Pancreas	3 (8)	3 (9)	3 (8)	7 (16)	5 (11)	4 (52)	1.62 (0.65–4.05)
All gastrointestinal (ICD7 151–157)	20 (59)	22 (57)	19 (56)	28 (68)	27 (66)	23 (306)	1.34 (0.94–1.91)
All respiratory (ICD7 160–163)	15 (44)	14 (35)	14 (43)	20 (48)	14 (33)	15 (203)	0.92 (0.58–1.44)
Prostate	18 (53)	19 (50)	19 (56)	19 (47)	24 (57)	20 (263)	1.27 (0.87–1.85)
Kidney	3 (9)	4 (11)	3 (9)	5 (12)	7 (16)	4 (57)	2.19 (0.97–4.98)
Urinary tract	7 (22)	6 (16)	8 (23)	9 (21)	11 (27)	8 (109)	1.50 (0.85–2.63)
All genito-urinary (ICD7 177–181)	29 (87)	30 (78)	30 (90)	33 (80)	42 (101)	32 (436)	1.39 (1.04–1.85) ←
Melanoma	3 (10)	3 (7)	4 (11)	6 (15)	3 (8)	4 (51)	0.97 (0.38–2.47)
Non-melanoma skin	6 (19)	9 (22)	8 (24)	8 (19)	13 (32)	9 (116)	1.98 (1.12–3.51) ←
Central nervous system	2 (6)	4 (10)	3 (8)	3 (7)	2 (6)	3 (37)	1.20 (0.39–3.74)
Haematopoietic and lymphatic	5 (15)	10 (25)	10 (29)	6 (15)	8 (20)	8 (104)	1.65 (0.84–3.23)
All other	5 (16)	7 (17)	7 (20)	7 (16)	11 (26)	7 (95)	2.10 (1.12–3.93)
Total	91 (271)	100 (257)	97 (294)	112 (275)	126 (304)	104 (1401)	1.36 (1.15–1.60)

“Although it was significant, the excess risk of cancer and of mortality from cancer associated with high blood pressure was not large in comparison with that of death from cardiovascular disease”

Obesity, Hypertension, and the Risk of Kidney Cancer in Swedish Men

VARIABLE	NO. OF MEN IN COHORT (N=363,992)	FOLLOW-UP person-yr	RENAL-CELL CANCER		RENAL-PELVIS CANCER	
			NO. OF MEN WITH CANCER	RELATIVE RISK (95% CI)	NO. OF MEN WITH CANCER	RELATIVE RISK (95% CI)
Smoking status						
Nonsmoker	148,206	2,129,536	180	1.0 (—)	18	1.0 (—)
Former smoker	51,638	909,630	145	1.3 (1.0–1.6)	19	1.6 (0.9–3.1)
Current smoker	138,332	2,289,228	334	1.6 (1.3–1.9)	82	3.5 (2.1–5.8)
Unknown	25,816	455,494	100	1.6 (1.2–2.0)	17	2.6 (1.3–5.0)
Body-mass index						
≤20.75	45,073	705,242	32	1.0 (—)	15	1.0 (—)
20.75–21.90	45,131	707,289	46	1.2 (0.7–1.8)	8	0.4 (0.2–1.0)
21.91–22.85	45,057	710,225	43	0.9 (0.6–1.5)	13	0.6 (0.3–1.3)
22.86–23.80	46,516	741,832	78	1.4 (0.9–2.1)	13	0.5 (0.2–1.1)
23.81–24.76	44,916	720,615	107	1.6 (1.1–2.4)	22	0.8 (0.4–1.5)
24.77–25.95	45,987	744,218	102	1.3 (0.8–1.9)	23	0.7 (0.4–1.3)
25.96–27.75	45,499	735,804	156	1.7 (1.1–2.5)	22	0.6 (0.3–1.1)
≥27.76	45,813	718,663	195	1.9 (1.3–2.7)	20	0.5 (0.2–1.0)
P for trend				<0.001		0.25
Diastolic blood pressure						
<70 mm Hg	40,407	540,097	12	1.0 (—)	6	1.0 (—)
70–79 mm Hg	110,461	1,695,116	96	1.4 (0.8–2.5)	22	0.6 (0.2–1.5)
80–89 mm Hg	139,998	2,317,216	273	1.7 (0.9–3.0)	49	0.6 (0.2–1.4)
90–99 mm Hg	57,060	974,597	272	2.1 (1.2–3.9)	46	0.7 (0.3–1.8)
100–109 mm Hg	11,627	187,114	78	2.3 (1.2–4.4)	10	0.6 (0.2–1.9)
≥110 mm Hg	4,439	69,748	28	2.2 (1.1–4.5)	3	0.6 (0.1–2.4)
P for trend				<0.001		0.74
Systolic blood pressure						
<120 mm Hg	39,010	554,138	28	1.0 (—)	11	1.0 (—)
120–129 mm Hg	100,884	1,561,807	103	1.1 (0.7–1.7)	28	0.8 (0.4–1.7)
130–139 mm Hg	108,165	1,754,399	192	1.5 (1.0–2.2)	29	0.6 (0.3–1.2)
140–149 mm Hg	67,661	1,122,128	168	1.4 (0.9–2.1)	27	0.6 (0.3–1.3)
150–159 mm Hg	27,361	458,505	124	1.6 (1.1–2.4)	20	0.7 (0.3–1.5)
≥160 mm Hg	20,911	332,911	144	1.7 (1.1–2.6)	21	0.7 (0.3–1.5)
P for trend				0.007		0.91

*All models included age, smoking status, body-mass index (the weight in kilograms divided by the square of the height in meters), and diastolic blood pressure. CI denotes confidence interval.

Hypertension and risk of renal cancer: interaction with obesity

363,992 Swedish men who underwent at least one physical examination from 1971 to 1992
Followed until death or the end of 1995

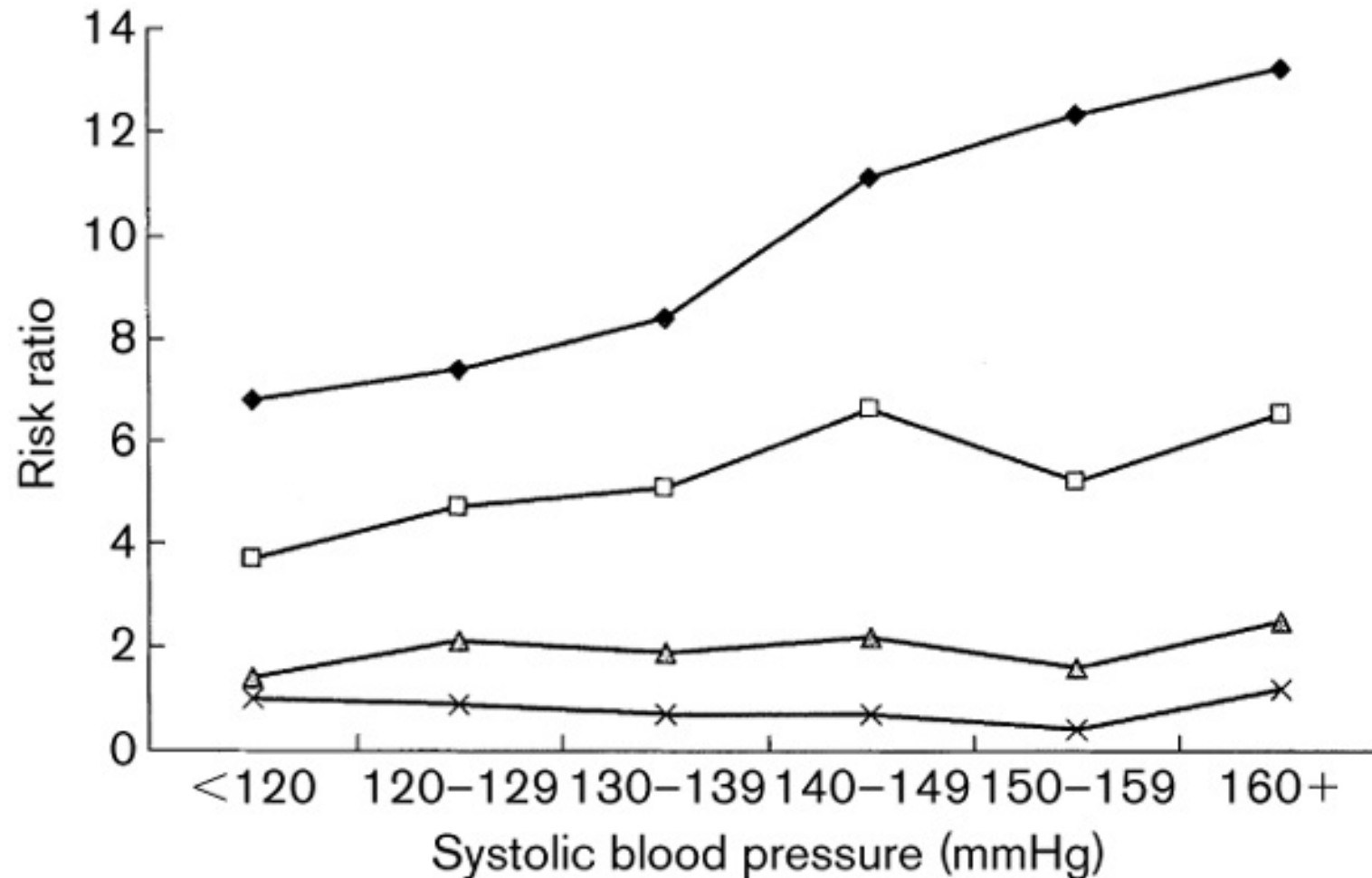
BODY-MASS INDEX†	DIASTOLIC BLOOD PRESSURE (mm Hg)					
	≤79		80–99		≥100	
	no. with cancer	relative risk (95% CI)	no. with cancer	relative risk (95% CI)	no. with cancer	relative risk (95% CI)
≤22.85	33	1.0 (—)	70	1.3 (0.9–2.0)	4	1.2 (0.4–3.3)
22.86–25.95	40	1.2 (0.8–2.0)	182	1.8 (1.2–2.6)	24	2.3 (1.4–4.0)
≥25.96	26	1.8 (1.1–3.1)	218	2.3 (1.6–3.4)	53	2.7 (1.7–4.2)

* Men in whom cancer was diagnosed during the first five years of follow-up and the person-years the cohort accumulated during that period were excluded. All relative risks have been adjusted for age and smoking. CI denotes confidence interval.

† Body-mass index was calculated as the weight in kilograms divided by the square of the height in meters.

Does hypertension increase mortality risk from lung cancer?

A prospective cohort study on smoking, hypertension and lung cancer risk among Korean men



Hypertension is associated with an increased risk of cancer mortality in a meta-analysis (1966-2000)

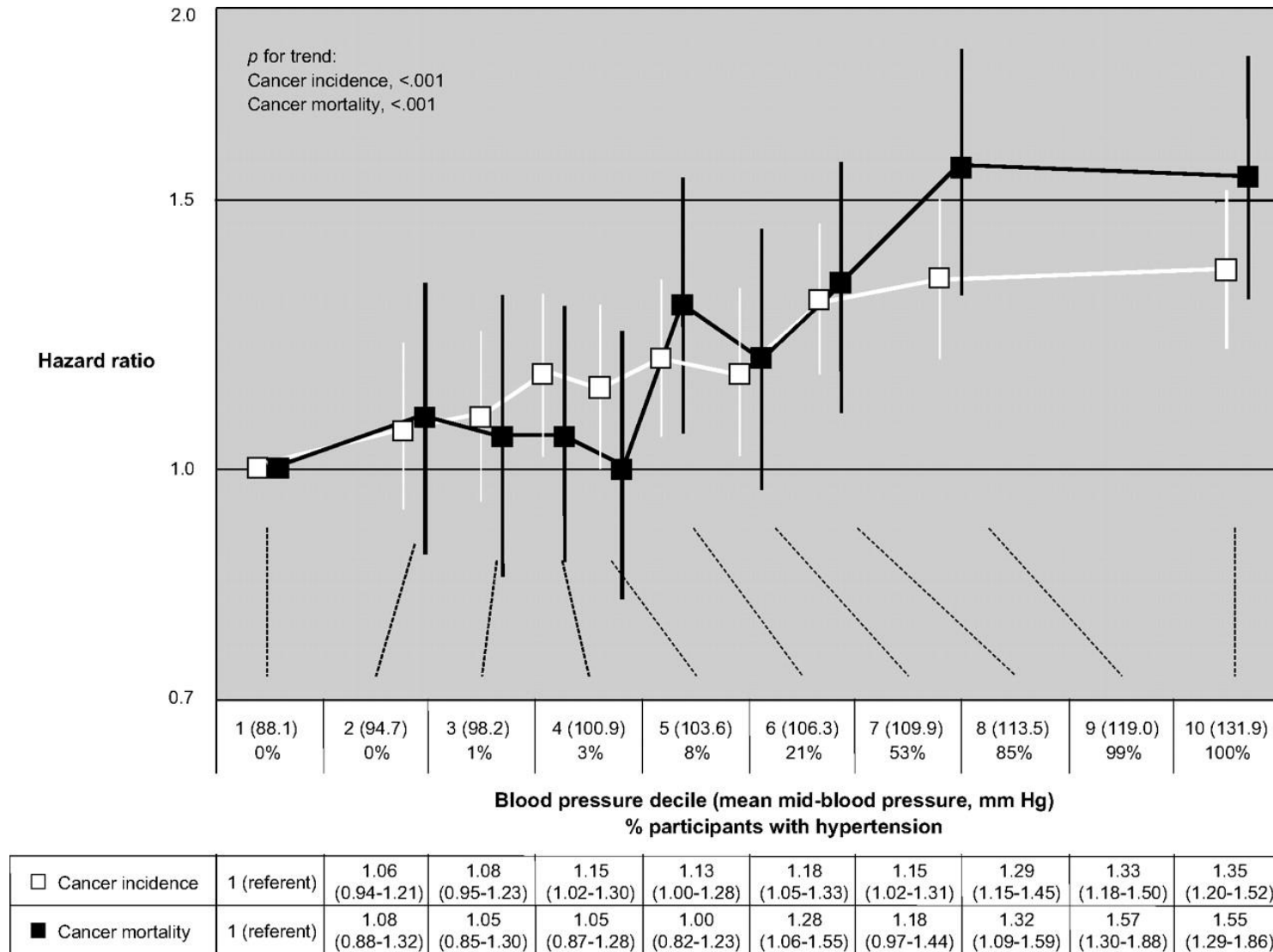
Ex: Hypertension and renal cell carcinoma

First Author (Reference)	Cases (n with Hypertension/n without Hypertension)	Controls (n with Hypertension /n without Hypertension)	Odds Ratio (95% Confidence Interval)	Adjusted Odds Ratio (95% Confidence Interval)*
Yu (36)	39/119	28/130	1.52 (0.85–2.72)	M: 1.5 (0.4–5.2) F: 1.9 (0.4–9.4)
McCredie (9)	203/286	178/345	1.38 (1.06–1.79)	1.8 (1.3–2.3)
Finkel (19)	143/48	115/76	1.97 (1.24–3.12)	
Kreiger (17)	90/428	146/1235	1.78 (1.32–2.39)	M: 1.4 (0.6–2.3) F: 1.3 (0.7–2.3)
Hiatt (20)	45/212	31/226	1.55 (0.92–2.61)	
Mellemgaard (18)	105/263	77/319	1.65 (1.17–2.35)	M: 1.8 (1.0–2.7) F: 1.8 (1.1–3.2)
Weinmann (21)	94/112	95/197	1.74 (1.18–2.56)	1.5 (0.63–3.3)
Muscat (33)	247/541	195/584	1.37 (1.09–1.72)	M: 1.9 (1.01–3.5) F: 3.2 (1.3–7.7)
McLaughlin (11)	562/1120	552/1722	1.57 (1.36–1.80)	1.7 (1.4–1.9)
Chow (12)	180/247	221/444	1.46 (1.13–1.90)	1.5 (1.1–1.90)
Liaw (37)	145/293	124/321	1.28 (0.95–1.73)	1.3 (1.0–1.8)
Yuan (34)	535/669	329/875	2.13 (1.79–2.53)	2.2 (1.8–2.6)
Shapiro (35)	130/108	252/364	1.74 (1.27–2.38)	M: 1.3 (0.7–2.5) F: 2.5 (1.2–5.1)
Pooled	2518/4446	2343/6838	1.62 (1.51–1.74)	1.75 (1.61–1.90) [†]

Systolic hypertension is associated with a 23% increased risk of cancer mortality

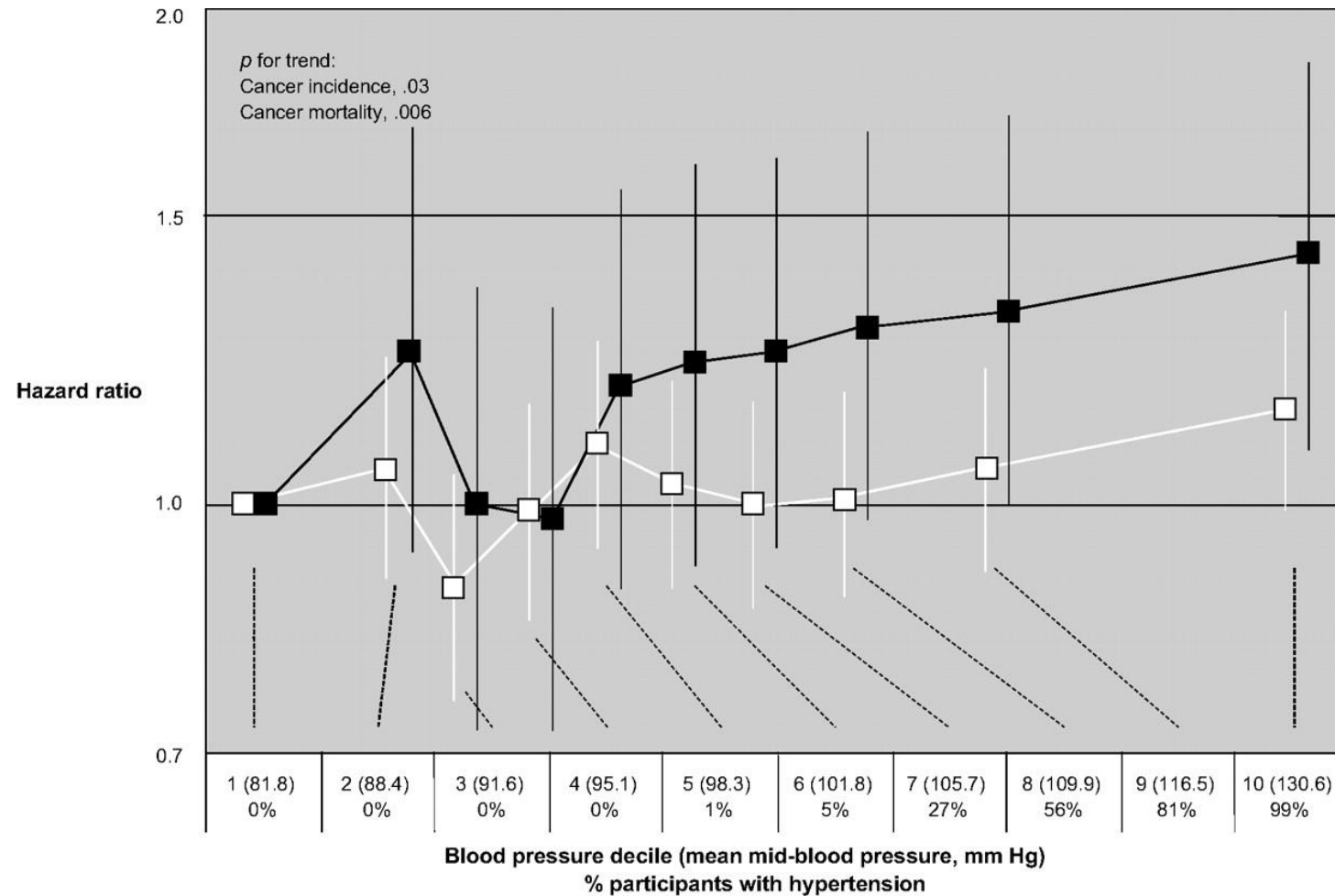
Blood Pressure and Risk of Cancer Incidence and Mortality in the Metabolic Syndrome and Cancer Project (Norway, Sweden and Austria, n= 577'799)

Men



Blood Pressure and Risk of Cancer Incidence and Mortality in the Metabolic Syndrome and Cancer Project (Norway, Sweden and Austria, n= 577'799)

Women



□ Cancer incidence	1 (referent)	1.05 (0.90-1.23)	0.89 (0.76-1.04)	0.99 (0.85-1.15)	1.09 (0.94-1.26)	1.03 (0.89-1.19)	1.00 (0.86-1.15)	1.01 (0.88-1.17)	1.05 (0.91-1.21)	1.14 (0.99-1.31)
■ Cancer mortality	1 (referent)	1.24 (0.92-1.67)	1.00 (0.73-1.36)	0.98 (0.73-1.32)	1.18 (0.89-1.56)	1.22 (0.92-1.61)	1.24 (0.94-1.63)	1.28 (0.98-1.68)	1.31 (1.00-1.72)	1.42 (1.08-1.86)

Shared pathogenic mechanisms in cardiovascular disease and cancer.

Some examples

Hypertension and CV disease

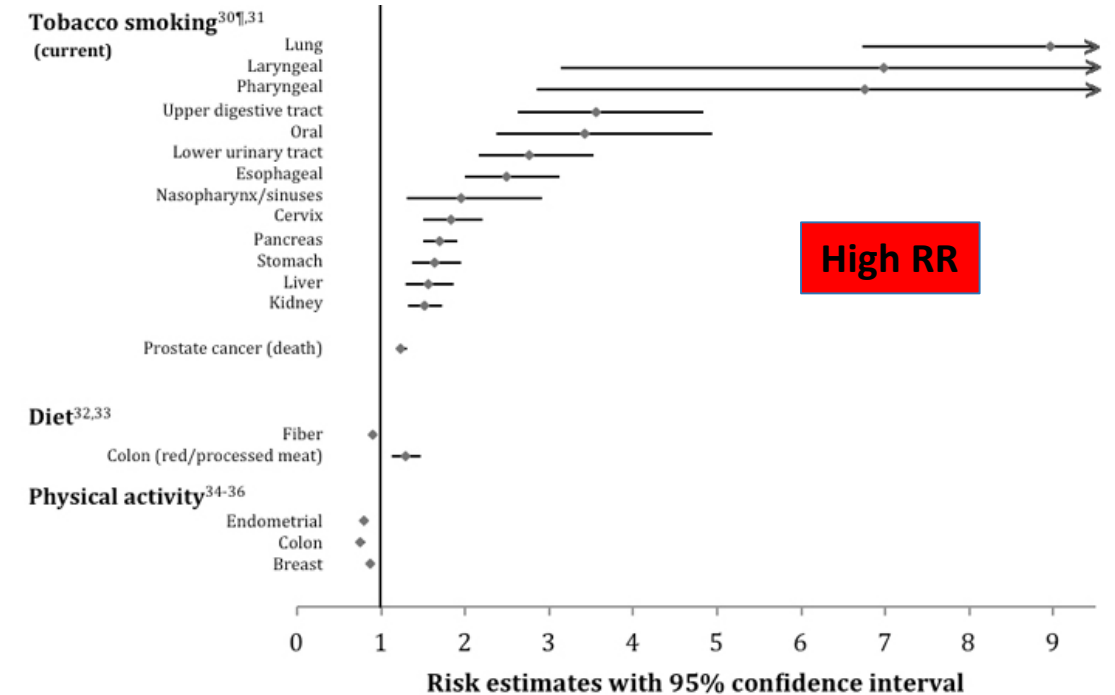
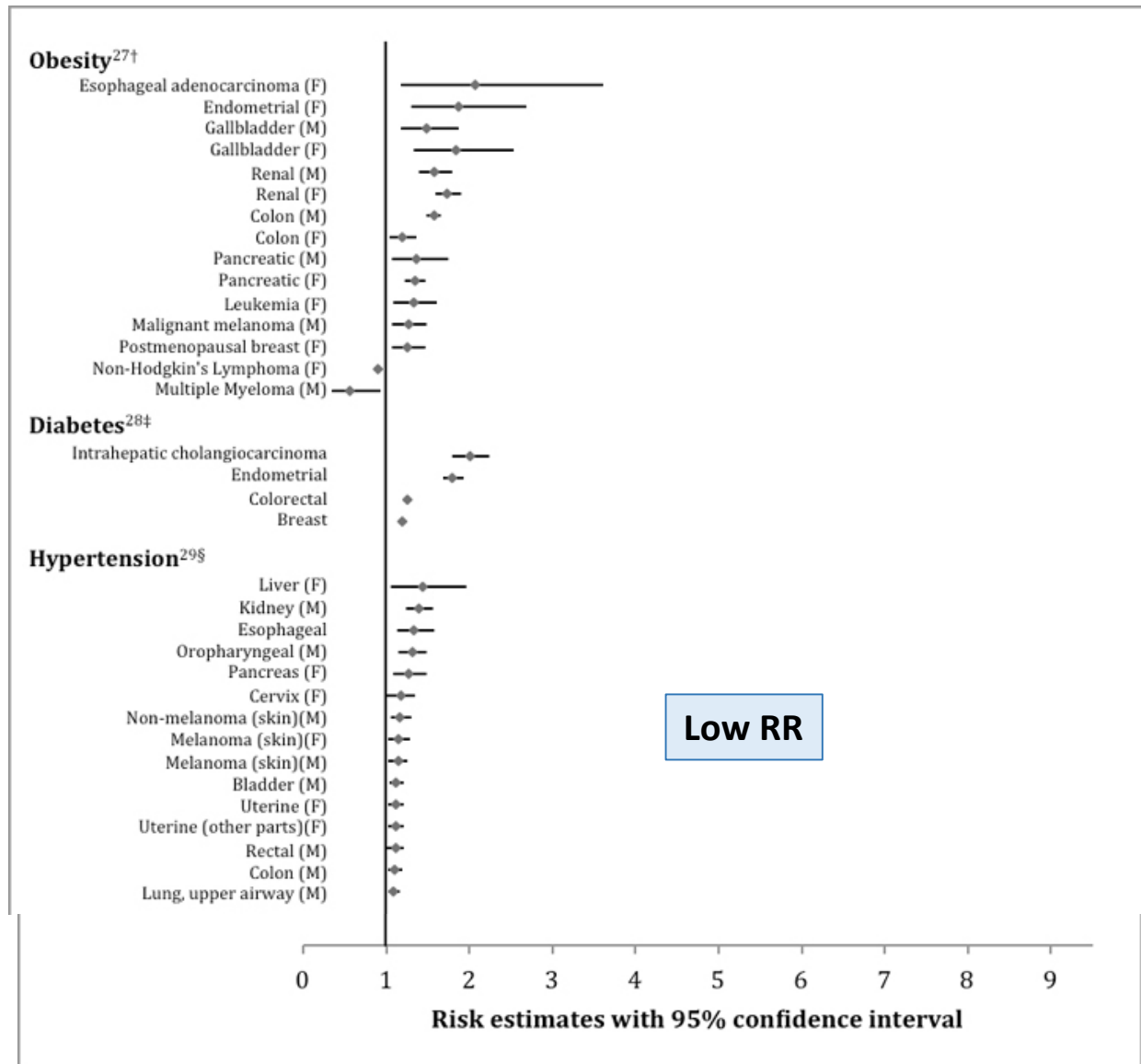
Increased response to some growth factors in VSMC
Increased apoptosis in adults but reduced in elderly
Shortening of telomeres
Increased proliferation (hormone-induced)
Inflammation
Oxidative stress and reactive oxygen species
Hormones (angiotensin II, (sex hormones, insulin and insulin-like growth factor [IGF] signaling, adipokines...)
Cytokines (IL6..)
Growth factors (VEGF)
Environmental toxics (pollution, ...)

Cancer

Alterations of growth factor receptors leading to a constitutive activation of tyrosine kinases
Shorten telomeres and increased telomerase activity
Increased cell proliferation
Inflammation
Oxidative stress
Hormones (angiotensin II, (sex hormones, insulin and insulin-like growth factor [IGF] signaling, adipokines...)
Cytokines (IL6..)
Growth factors
Environmental toxics (pollution, ...)

The biological basis of most cancers is as unresolved as the pathogenesis of essential hypertension

Shared Risk Factors in Cardiovascular Disease and Cancer.



Why we may overlook the impact of hypertension

The risk is actually small (usually 1.2–2.2)

Other factors that modify this risk, such as obesity and diabetes, may contribute with hypertension

Smoking may strongly enhance the biological impact of hypertension (positive interaction)

Increase in life expectancy with the reduction of CV disease mortality

Pollution and toxics

Conclusion 1: Hypertension and risk of cancer

There is a positive association between the level of BP and the risk of cancer, essentially renal

However, the strength is low, and there are strong interactions with other risk factors.

Thus, hypertension may be a **risk marker rather than a risk factor**

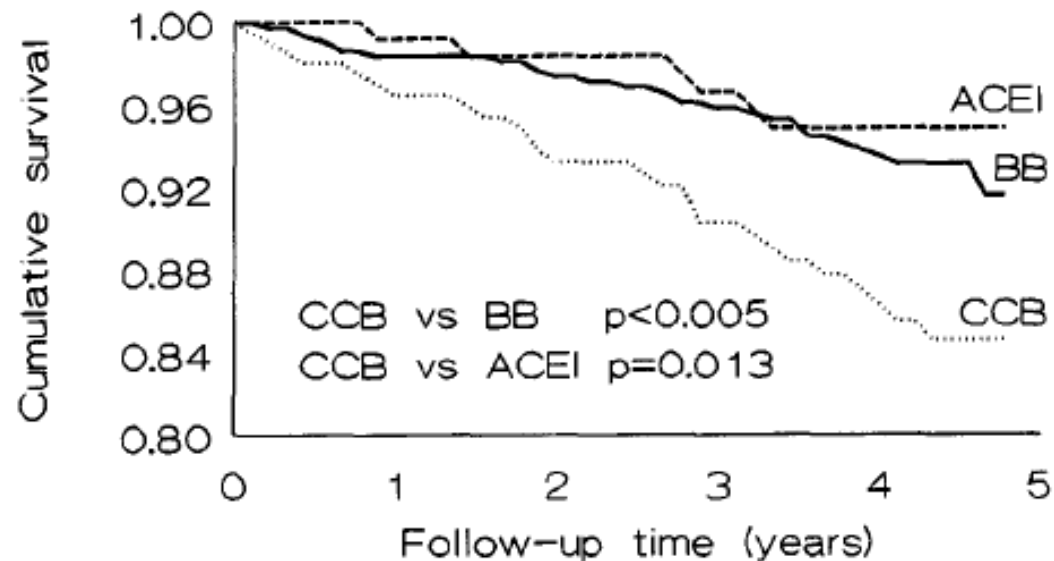
2) Is there an increased risk of cancer with antihypertensive drugs?

Hypertension drugs recalled because of cancer risk
TELES RELAY January 8, 2019



1996: the calcium channel blocker controversy

Drug Category	No. Using the Drug	All Cancers				Fatal Cancers			
		n	Rate	RR	95% CI	n	Rate	RR	95% CI
β -Blockers	424	28	16.9	1		12	7.1	1	
ACE inhibitors	124	6	12.2	0.73	0.30–1.78	1	2.0	0.32	0.04–2.49
Calcium channel blockers	202	27**†	37.0	2.02	1.16–3.54	11†	14.5	2.04	0.65–4.89
Verapamil	65	10*†	41.0	2.46	1.17–5.17	2	7.8	1.15	0.25–5.29
Nifedipine	61	10*†	49.3	2.34	1.09–5.03	6***†	28.2	3.74	1.30–10.78
Diltiazem	76	7	25.1	1.40	0.59–3.28	3	10.5	1.52	0.41–5.68



Pahor M, et al, Lancet 1996 and
Am J Hypertens 1996;9:695–699

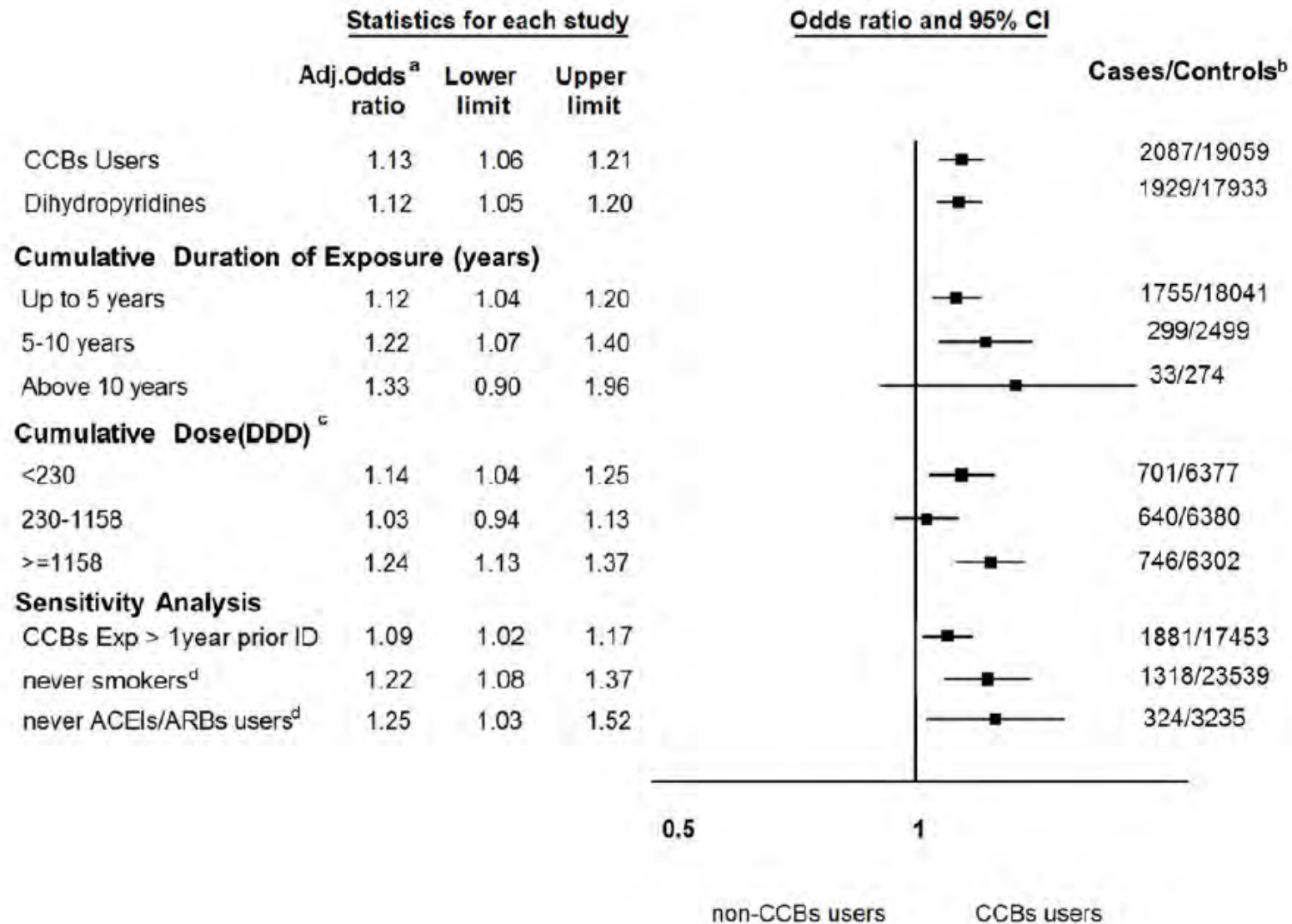
Risk of all types of cancer in the calcium channel blocker (CCB) cohort compared to the non-CCB and the non-CCB antihypertensive (AHT) drugs cohorts

Cohort	Number of cancers	Number of person-years	Cancer incidence rates (per 1000 person-years)	CCB vs non-CCB		CCB vs AHT	
				Crude HR (95% CI)	Adjusted HR	Crude HR (95% CI)	Adjusted HR
CCB	14 588	883 803	16.51	1.03 (1.01 to 1.05)	0.88 (0.86 to 0.89)*	1.56 (1.53 to 1.61)	1.01 (0.98 to 1.04)
Non-CCB	43 992	2 792 948	15.75	1.00 (reference)	1.00 (reference)	–	–
AHT	9754	918 801	10.62	–	–	1.00 (reference)	1.00 (reference)

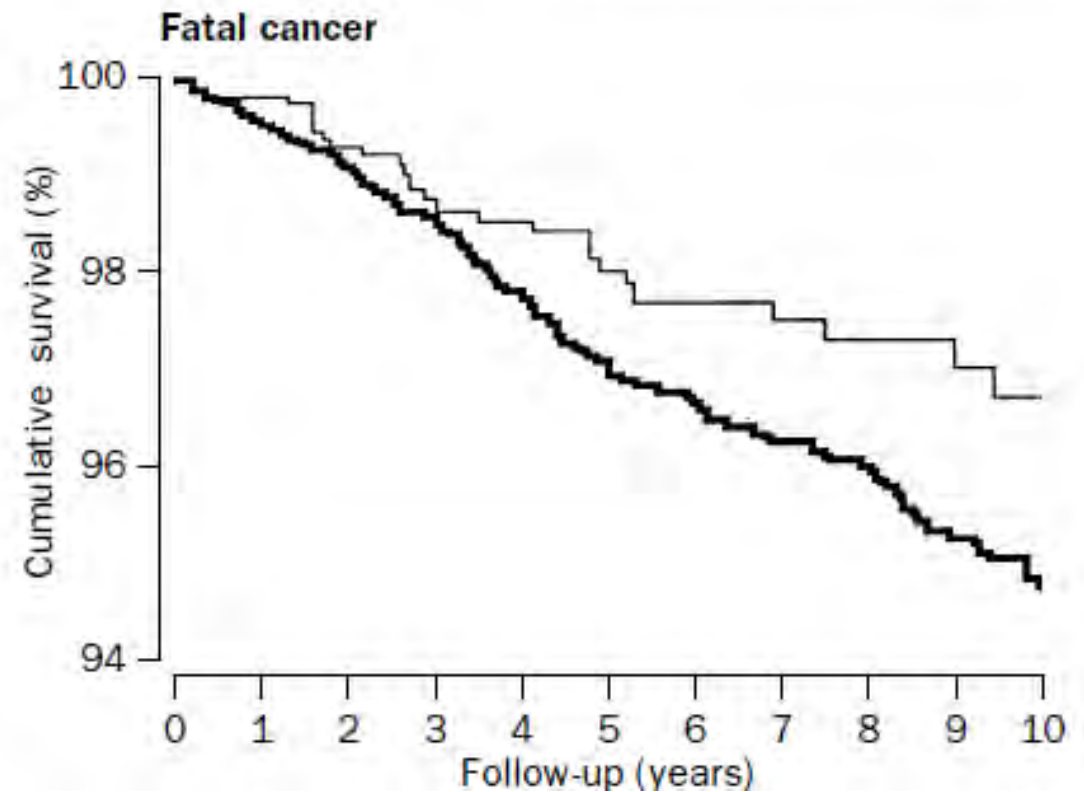
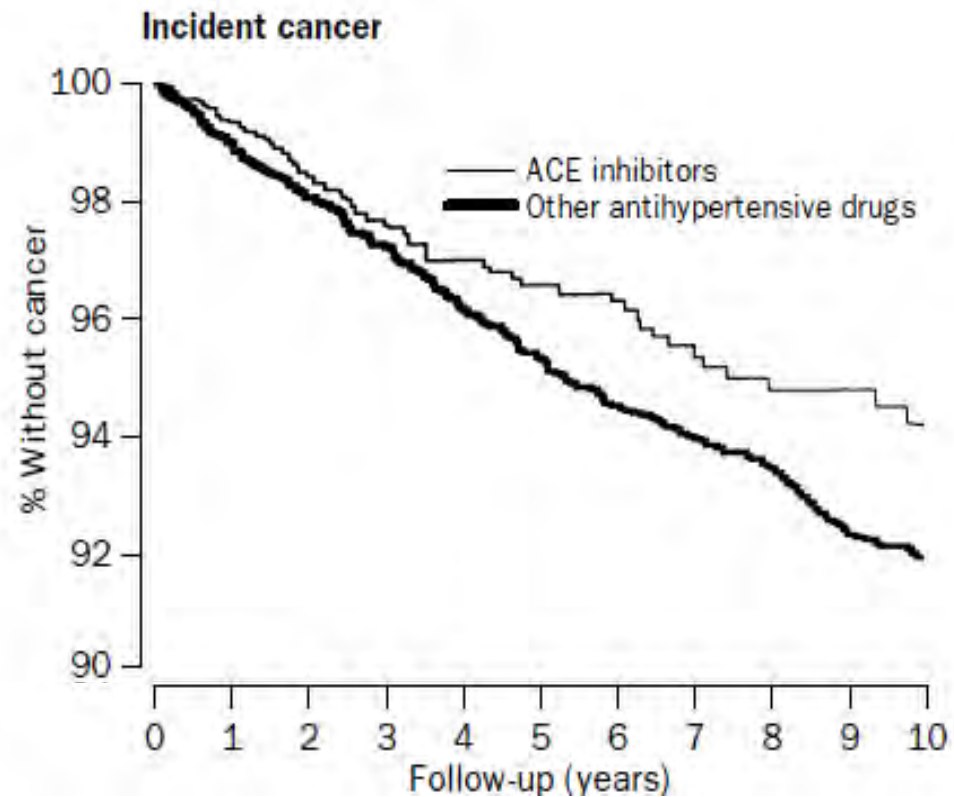
*p<0.001. HR obtained from multivariate Cox proportional hazard analyses including age at index date, gender, smoking status, body mass index, alcohol consumption, diagnoses of diabetes, hypertension, arrhythmia, angina or heart failure, and use of statins or aspirin.

No increased risk in breast, prostate and colon cancers with CCB in this analysis

Calcium channel blockers and risk of lung cancer



Are ACE inhibitors protective against the risk of cancer ?



A new paper in the BMJ in 2018

Angiotensin converting enzyme inhibitors and risk of lung cancer: population based cohort study

Blánaid M Hicks,^{1,2,3} Kristian B Filion,^{1,2,4} Hui Yin,¹ Lama Sakr,⁵ Jacob A Udell,^{6,7} Laurent Azoulay^{1,2,8}

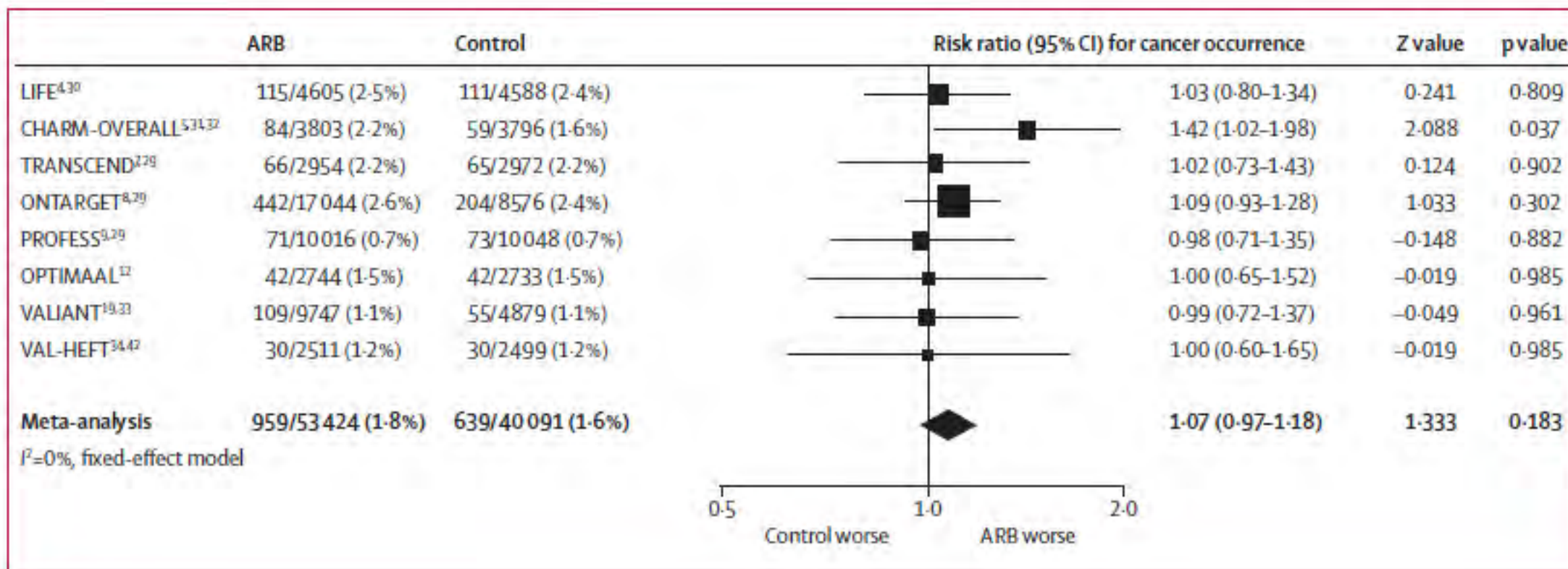
Exposure*	Events	Person years	Incidence rate (95% CI)†	Hazard ratio (95% CI)		P for trend
				Crude	Adjusted‡	
ARBs	266	213 557	1.2 (1.1 to 1.4)	1.00	1.00 (reference)	
ACEIs	3186	1 977 139	1.6 (1.6 to 1.7)	1.32	1.14 (1.01 to 1.29)	
Cumulative duration of ACEI use (years)						
≤5	2084	1 440 232	1.4 (1.4 to 1.5)	1.24	1.10 (0.96 to 1.25)	<0.001
5.1-10	905	457 309	2.0 (1.9 to 2.1)	1.44	1.22 (1.06 to 1.40)	
>10	197	79 598	2.5 (2.1 to 2.8)	1.63	1.31 (1.08 to 1.59)	
Time since first ACEI use (years)						
≤5	1617	1 158 441	1.4 (1.3 to 1.5)	1.24	1.11 (0.97 to 1.27)	<0.001
5.1-10	1155	647 103	1.8 (1.7 to 1.9)	1.33	1.14 (0.99 to 1.30)	
>10	414	171 596	2.4 (2.2 to 2.7)	1.62	1.29 (1.10 to 1.51)	

Main limitations of this observation

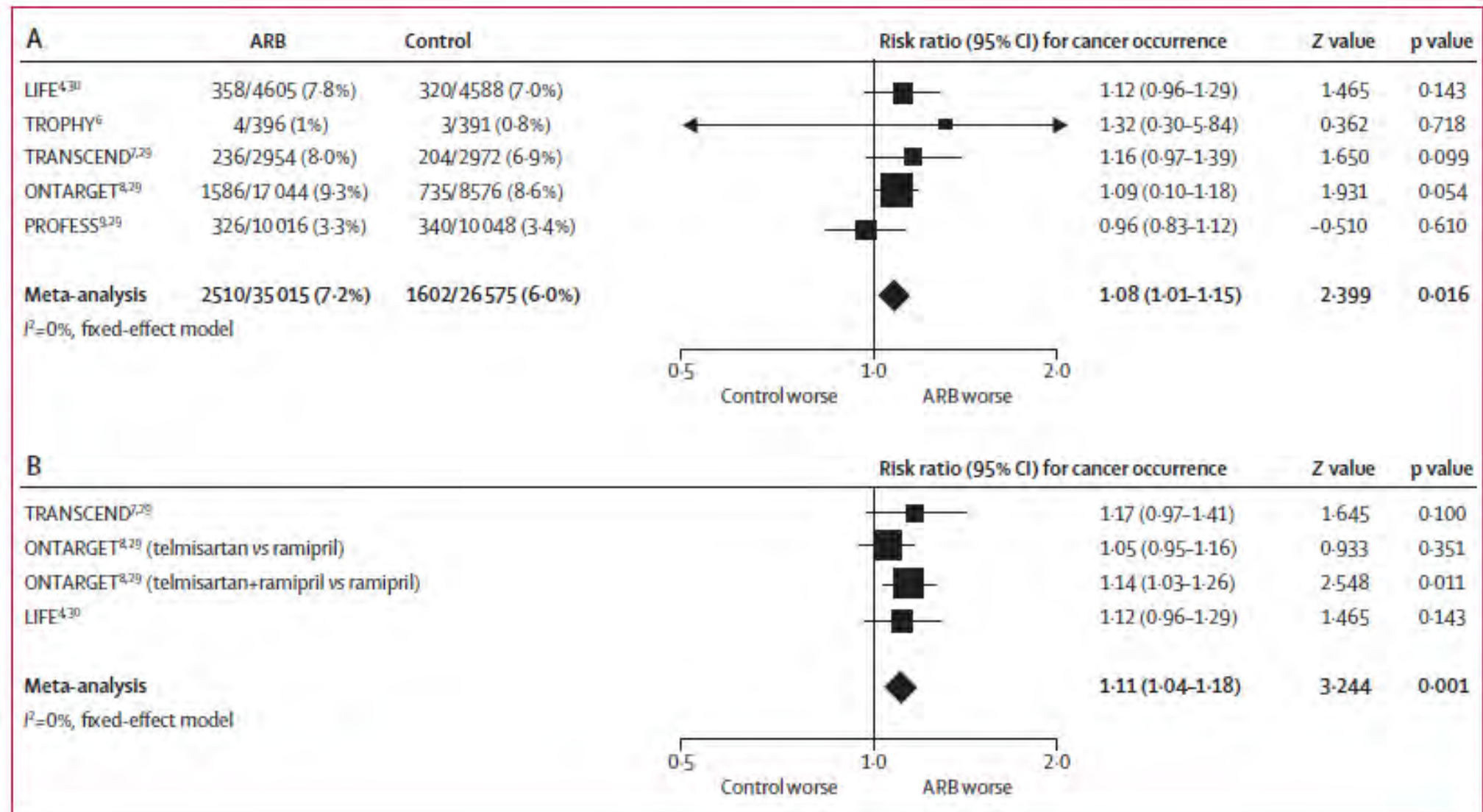
1. *Smoking status*: the recorded rate of smoking evaluated from structured fields of electronic clinical records might be an underestimate
2. There were statistically significant *differences in chronic diseases* between cases and controls
3. No impact in the non-smoker population
4. There is a potential for *reverse causality* bias because more patients with a cough will receive CCBs and not ACE inhibitors, whereas a cough may be an early symptom of undiagnosed lung cancer at that period.
5. In addition, the database *lacks information on certain lung cancer risk factors*, such as occupational exposures to carcinogens, exposure to second-hand smoking, prior radiation exposure, socioeconomic status, and family history of lung cancer.

2010: the ARB controversy

Cancer deaths reported in randomized controlled trials of ARBs



Cancer occurrence reported in all included trials of angiotensin-receptor blockers (A) and trials in which cancer was a prespecified endpoint (B)

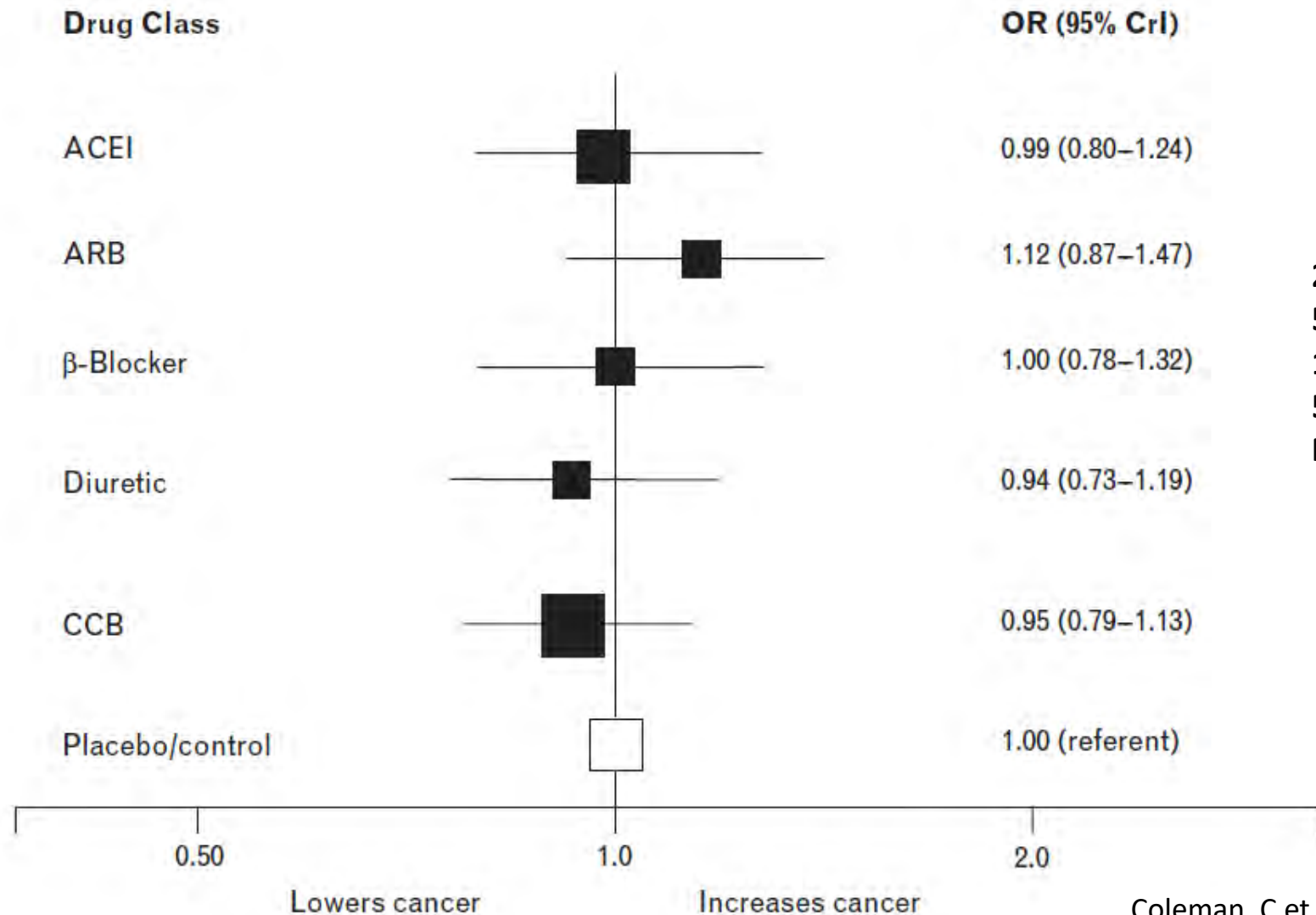


ARBs and risk of cancer: a correction to Sipahi's publication

In VALUE, 510 of 7649 cancer cases were reported with the ARB valsartan (6.7%) compared with 591 of 7596 cases reported with the calcium-channel blocker amlodipine (7.8%). With 15 245 patients followed up for several years in the large VALUE clinical trial, this finding argues against an increased cancer risk associated with ARB therapy.

If the VALUE data are appropriately included in Sipahi and colleagues'¹ meta-analysis, the event numbers become **1870 of 24 146 (7.7%) versus 1853 of 24 123 (7.7%)**, and clearly show no difference in cancer rates between ARB and control therapies.

Antihypertensive medication and their impact on cancer incidence: a mixed treatment comparison meta-analysis of randomized controlled trials



27 studies
56 treatment arms
126 137 patients enrolled
5868 cancers identified
Mean duration 3.3 y

What about diuretics and the risk of cancer ?

Diuretic use has been associated essentially with:

Renal cancers

Skin cancers

Photosensitivity Due to Chlorothiazide and Hydrochlorothiazide

•Leonard C. Harber, M.D.[†], Alvin M. Lashinsky, M.D.[‡], and Rudolf L. Baer, M.D.[§]

NEJM, 1959

The action spectrum in photosensitization due to these drugs was shown to be in the wavelength range between 2750 Å and 3100 Å, i.e., **in the sunburn part of the ultraviolet spectrum.**

Antihypertensive Drugs and Lip Cancer in Non-Hispanic Whites

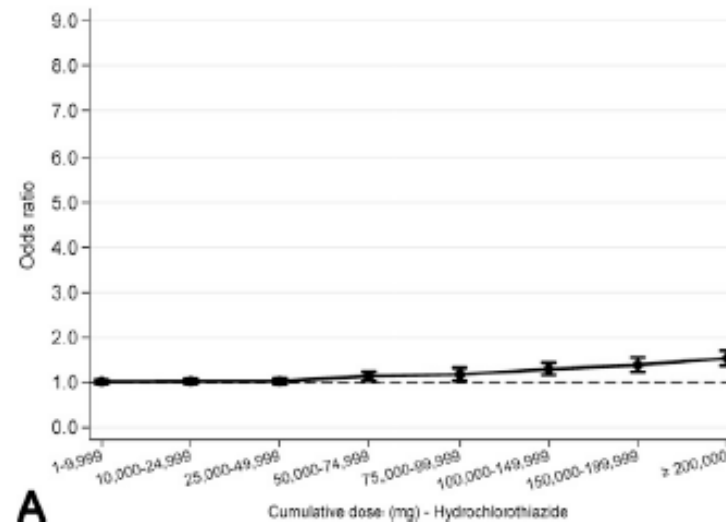
Kaiser Permanence
Prescriptions dispensed
and cancer occurrence
from August 1, 1994,
to February 29, 2008.

Table 5. ORs of Developing Lip Cancer According to the Amount of Drugs Dispensed, Measured in Years Supply, Regardless of Whether Other Drugs Were Given

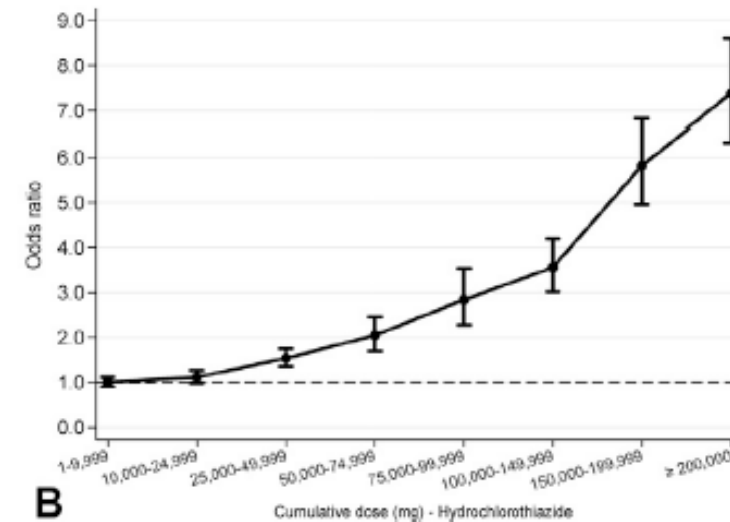
Variable	OR (95% CI) ^a		
	<1-Year Supply	1-Year to <5-Year Supply	≥5-Year Supply
→ Hydrochlorothiazide	0.98 (0.66-1.45)	2.03 (1.54-2.68)	4.22 (2.82-6.31)
Hydrochlorothiazide- triamterene	0.91 (0.60-1.39)	1.87 (1.37-2.57)	2.82 (1.74-4.55)
Lisinopril	1.04 (0.74-1.46)	1.60 (1.25-2.04)	1.42 (0.95-2.13)
→ Nifedipine	1.77 (1.20-2.59)	2.26 (1.58-3.23)	2.50 (1.29-4.84)
Atenolol	0.88 (0.62-1.26)	0.88 (0.63-1.21)	1.93 (1.29-2.91)
Atenolol only ^b	0.68 (0.30-1.55)	0.42 (0.15-1.14)	0.54 (0.07-4.08)

Risk of non-melanoma skin cancers associated with HCTZ

Basal cell carcinoma



Squamous cell carcinoma



Observations:

- Low risk for basal cell carcinoma and higher for squamous cell carcinoma
- No data on UV exposure
- Population at higher risk of skin cancer (blond, light skin,...).
- To be confirmed in another population
- **Considérer la balance risque/bénéfice**

Hydrochlorothiazide use and risk of melanoma skin cancer

Melanoma	Cases. No.	Controls, No.	Adjusted OR (95% CI)	
			Model 1 ^a	Model 2 ^b
Superficial Spreading Melanoma				
Never used	12 494	126 216	1 [Reference]	1 [Reference]
Ever used	1287	11 594	1.13 (1.06-1.20)	1.13 (1.06-1.20)
High use (≥50 000 mg)	254	2268	1.14 (0.99-1.30)	1.11 (0.97-1.27)
Cumulative dose				
1-24 999 mg	783	7023	1.14 (1.05-1.23)	1.13 (1.05-1.23)
25 000-49 999 mg	250	2303	1.11 (0.97-1.27)	1.10 (0.96-1.27)
50 000-99 999 mg	140	1252	1.15 (0.96-1.38)	1.14 (0.95-1.37)
≥100 000 mg	114	1016	1.12 (0.91-1.36)	1.06 (0.87-1.30)
Test for trend	1287	11 594	P = .94	P = .73

>70% of melanomas

4-15% of melanomas

		Adjusted OR (95% CI)	
Cases. No.	Controls, No.	Model 1 ^a	Model 2 ^b
386	4198	1 [Reference]	1 [Reference]
114	802	1.57 (1.25-1.97)	1.58 (1.25-2.00)
28	177	1.72 (1.13-2.62)	1.61 (1.03-2.50)
58	476	1.32 (0.98-1.78)	1.35 (0.99-1.83)
28	149	2.22 (1.44-3.43)	2.30 (1.46-3.60)
11	99	1.25 (0.66-2.38)	1.09 (0.56-2.11)
17	78	2.26 (1.30-3.91)	2.24 (1.25-3.99)
114	802	P = .11	P = .16

Hydrochlorothiazide use and risk of melanoma skin cancer

			Adjusted OR (95% CI)	
	Cases, No.	Controls, No.	Model 1 ^a	Model 2 ^b
Nodular Melanoma				
Never used	1465	15 108	1 [Reference]	1 [Reference]
Ever used	230	1842	1.31 (1.12-1.53)	1.28 (1.09-1.49)
High use (≥50 000 mg)	68	351	2.13 (1.61-2.80)	2.05 (1.54-2.72)
Cumulative dose				
1-24 999 mg	119	1142	1.08 (0.88-1.32)	1.05 (0.86-1.29)
25 000-49 999 mg	43	349	1.24 (0.90-1.72)	1.17 (0.84-1.64)
50 000-99 999 mg	34	195	1.90 (1.30-2.78)	1.81 (1.23-2.67)
≥100 000 mg	34	156	2.34 (1.59-3.45)	2.26 (1.52-3.36)
Test for trend	230	1842	P = .01	P = .01

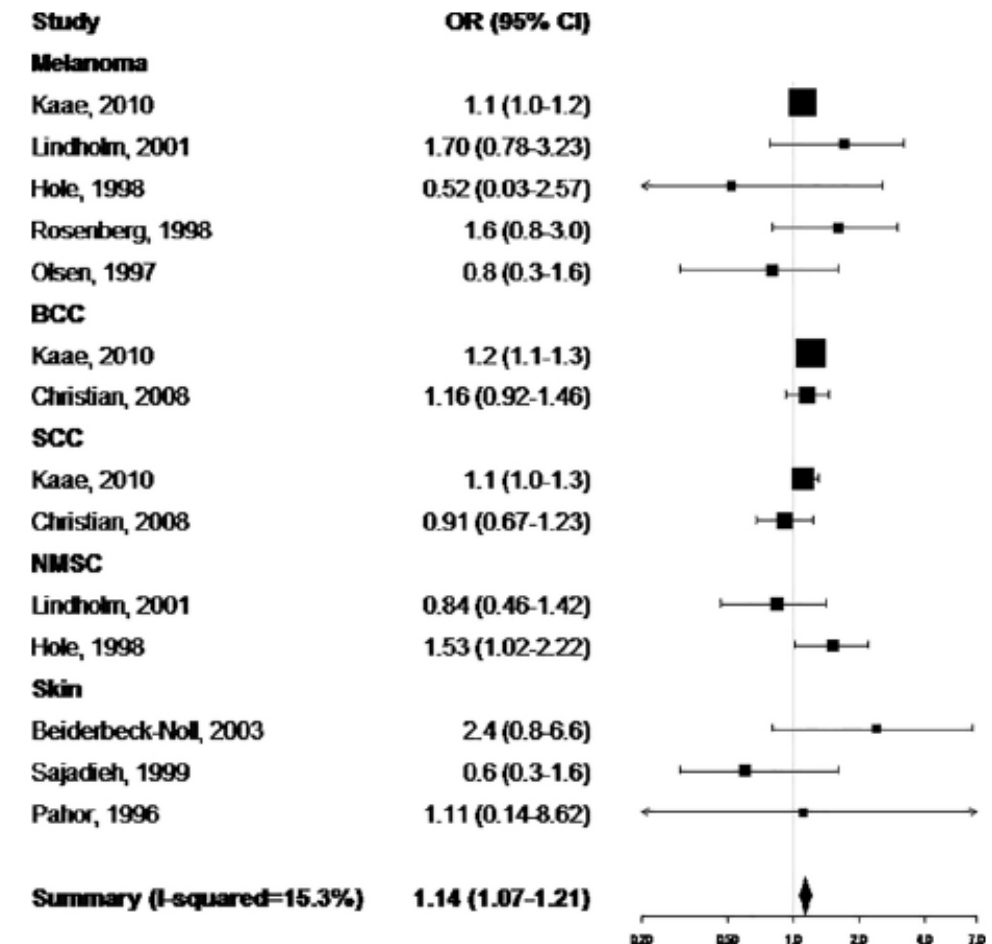
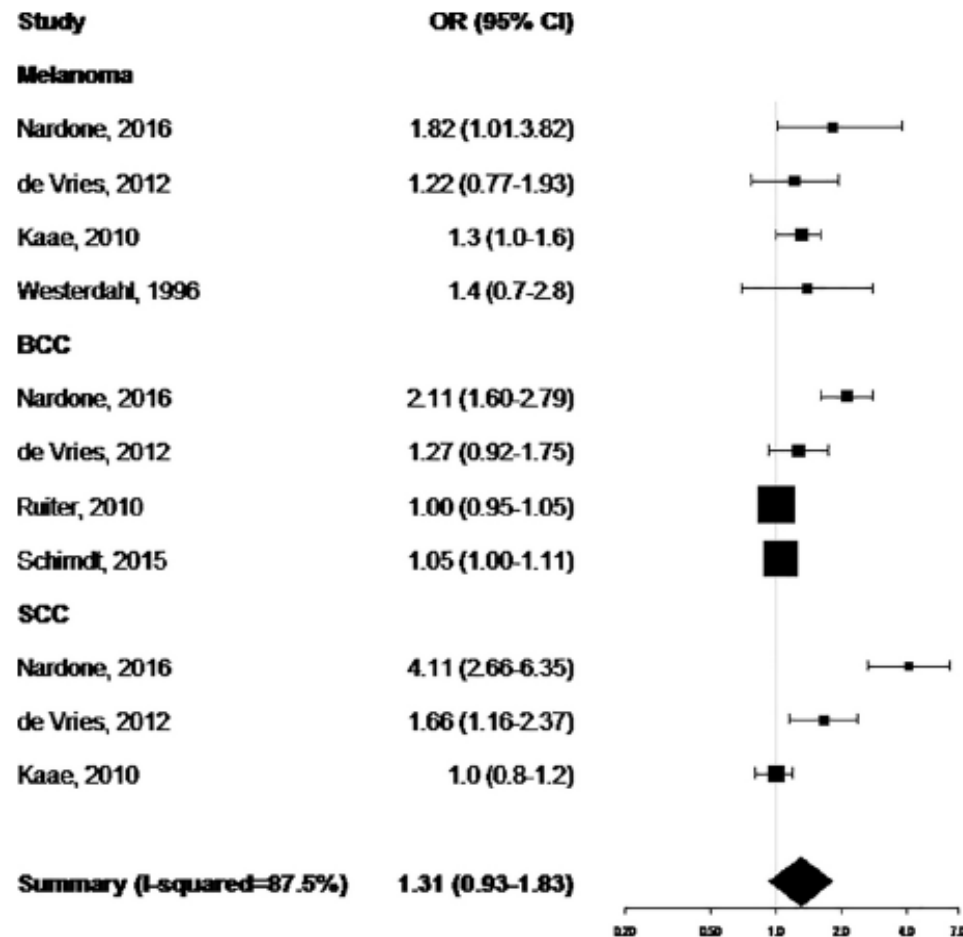
5% of melanomas

What should we do with HCTZ and the risk of skin cancer

1. A priori, no interruption of the treatment but inform patients.
2. Si high worry and history of skin cancer, switch to indapamide or chlorthalidone
3. Ask patient patients to check their skin regularly at home
4. Skin check by a physician at least once every two years.
5. Avoid excessive UV exposure: apply recommendations for the general prevention of skin cancers.

Anti-hypertensive drugs and skin cancer risk: a review of the literature and meta-analysis

Sara Gandini^a, Domenico Palli^b, Giuseppe Spadola^c, Benedetta Bendinelli^b, Emilia Cocorocchio^c, Ignazio Stanganelli^d, Lucia Miligi^e, Giovanna Masala^b, Saverio Caini^{b,*}



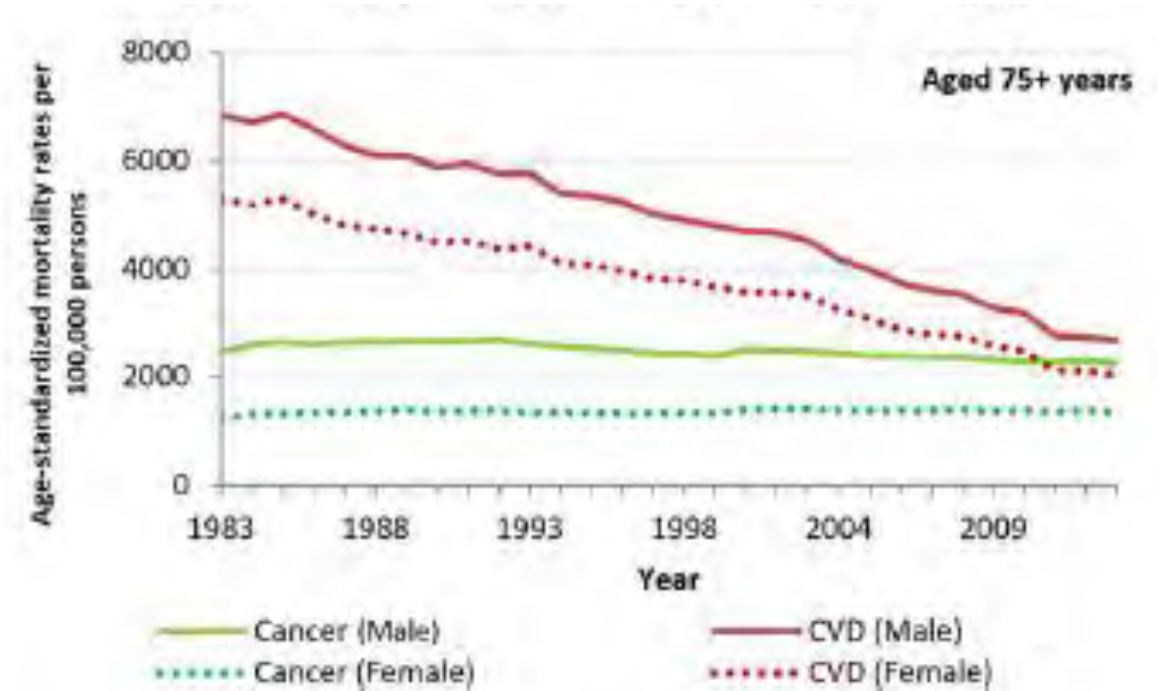
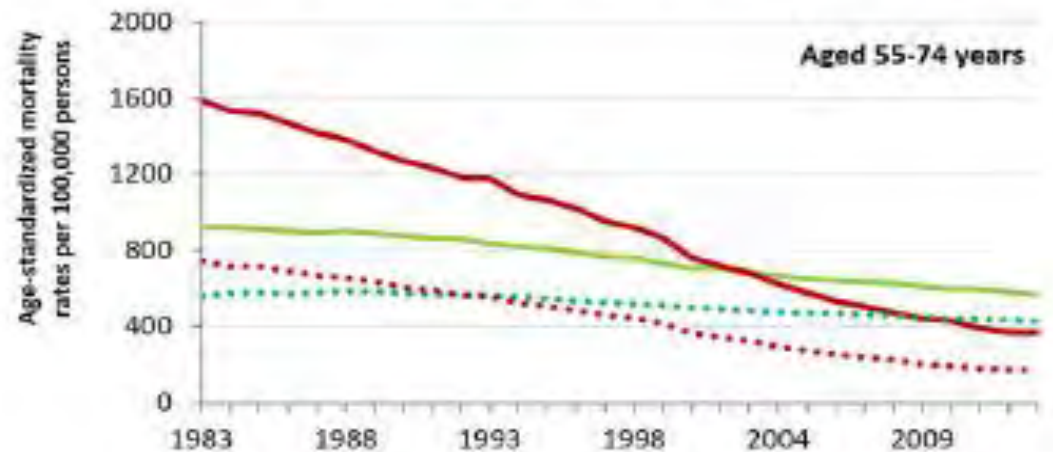
Bradford Hill criteria for causality

	Hypertension and cancer risk	Diuretics and skin cancer risk
1) Strength	+	++
2) Consistency	+	++
3) Specificity	+	+
4) Temporality	-	++
5) Biological gradient	++	++
6) Plausibility	+	++
7) Coherence	-	+
8) Experiment	-	-

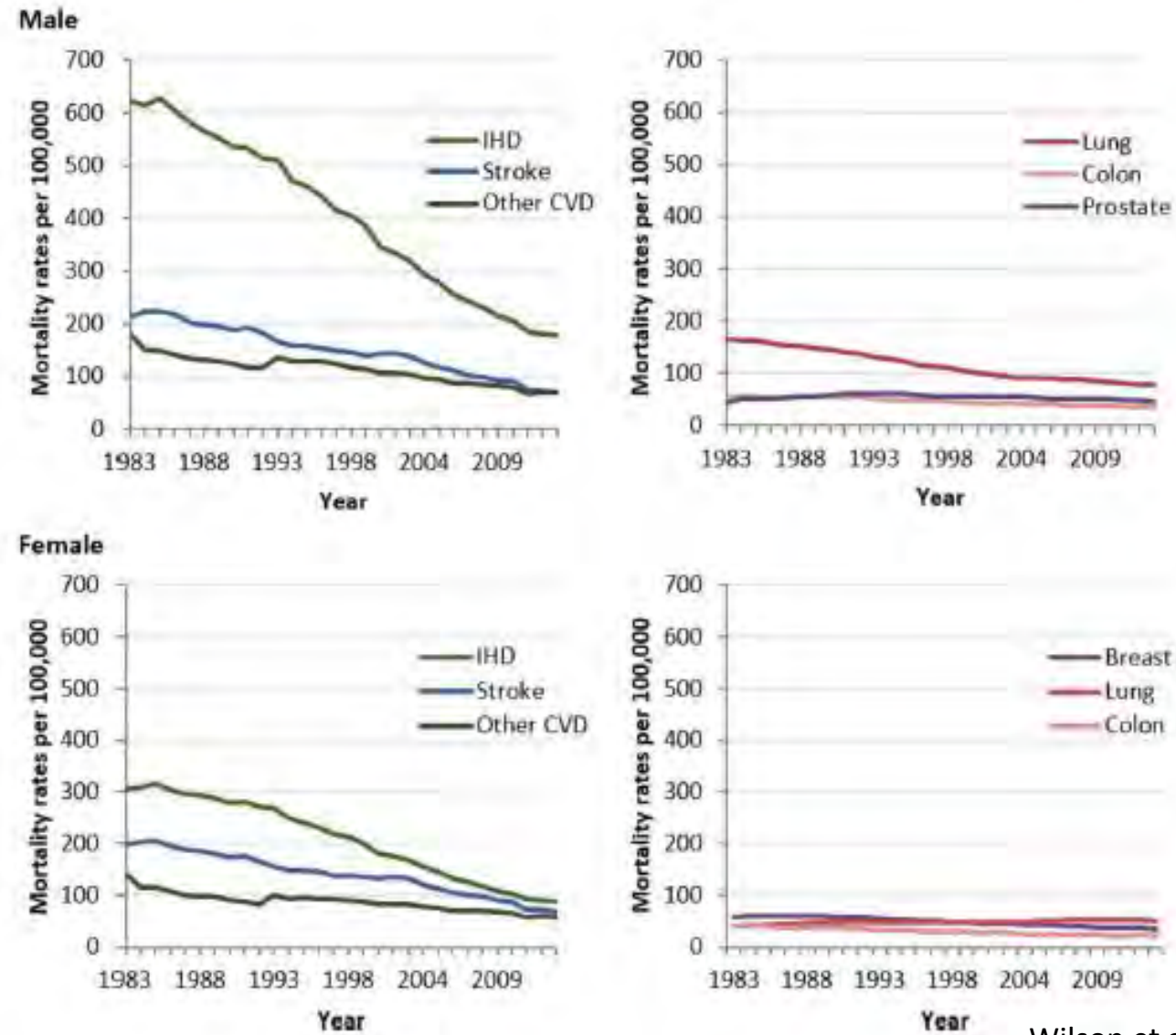
Age-standardized mortality trends for cancer (including benign) and cardiovascular diseases in the UK. Years 1983 to 2013



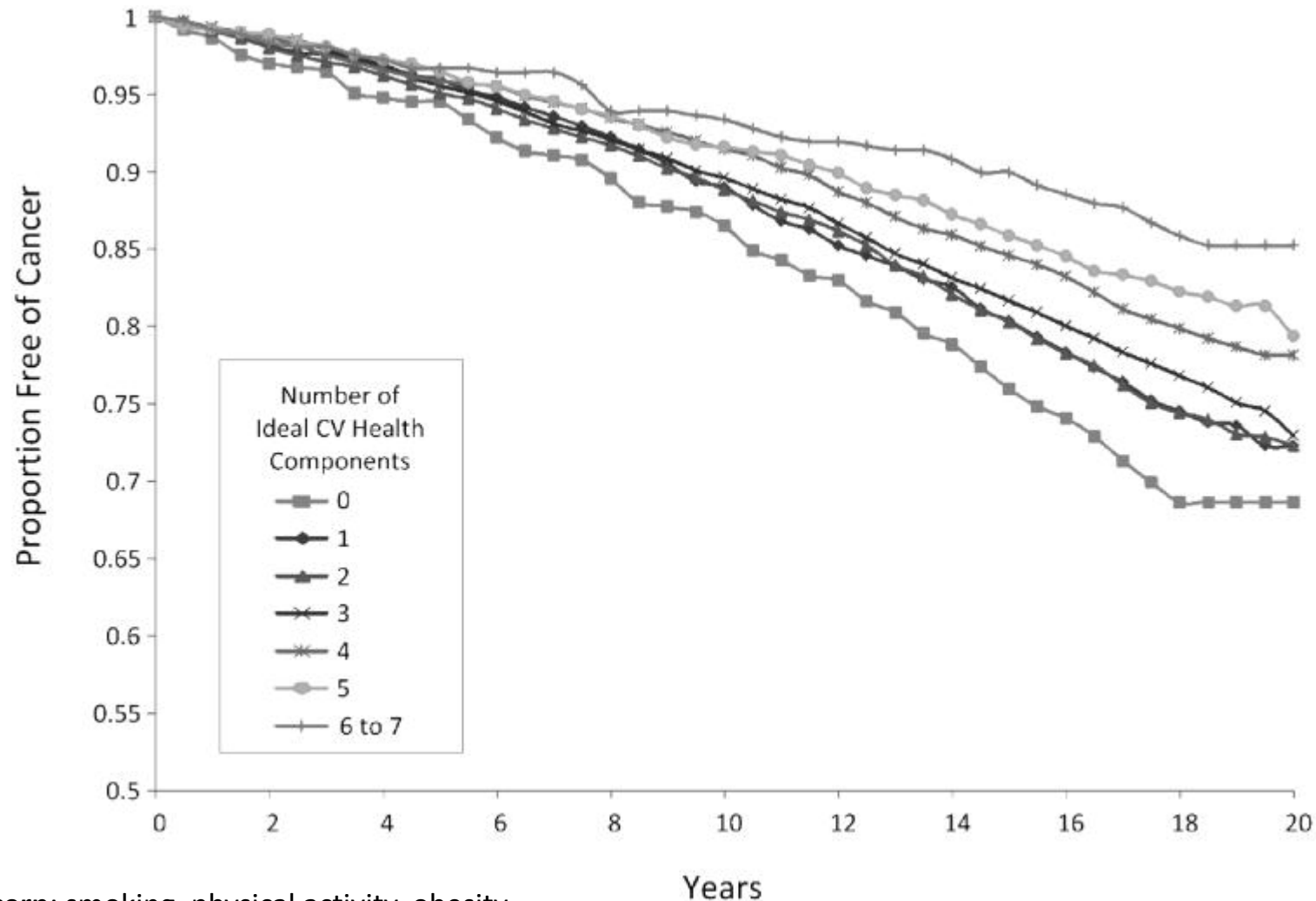
Age-standardized mortality trends for cancer and CVD by age group and sex.



Age-standardized mortality trends for IHD, stroke, other CVD, and lung, colon, breast, and prostate cancer



Ideal Cardiovascular Health is Inversely Associated with Incident Cancer: The Atherosclerosis Risk in Communities Study



Seven health behaviors concern: smoking, physical activity, obesity, dietary intake, total cholesterol, blood pressure and blood sugar

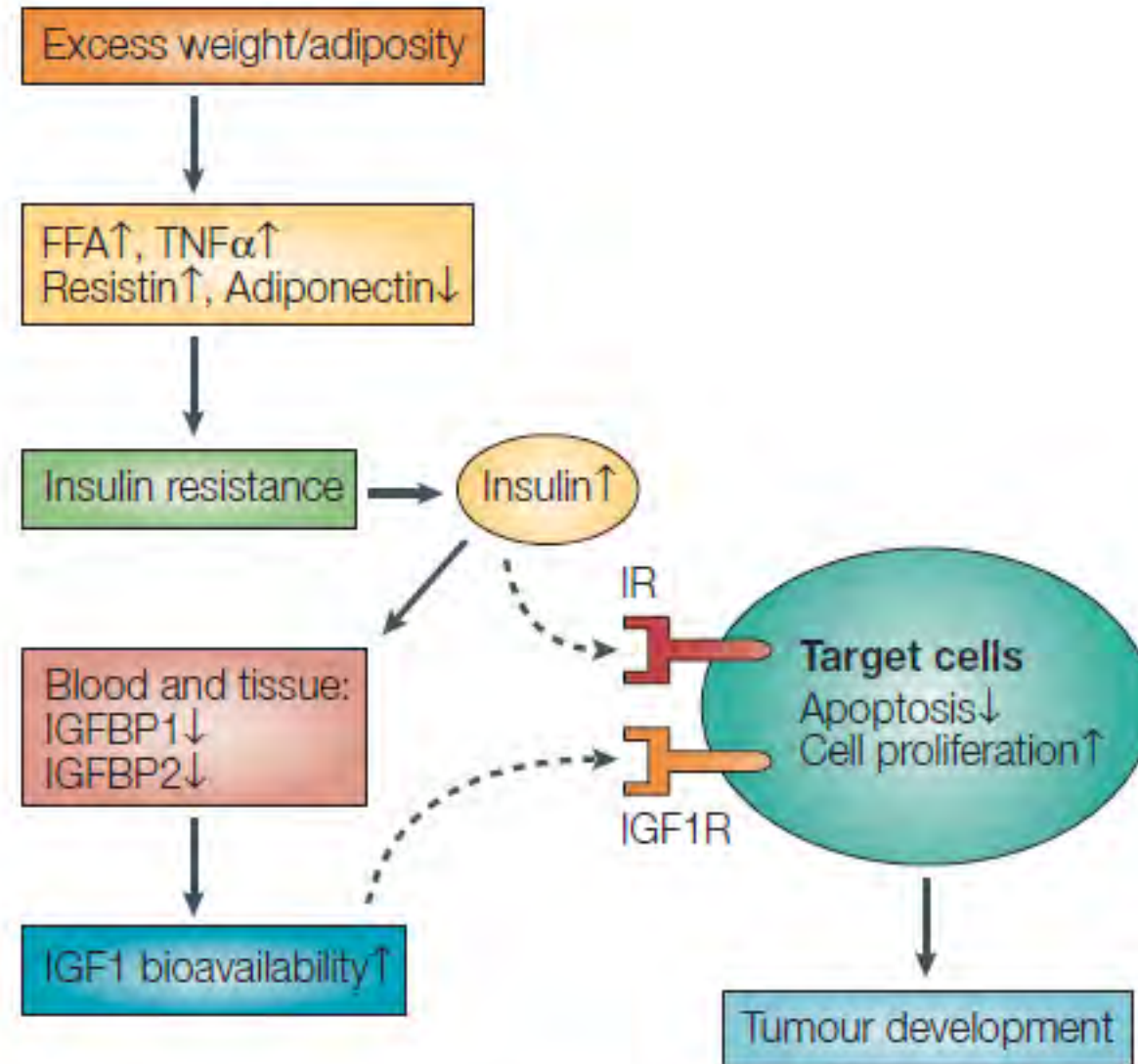
Conclusion

“Ruling out cancer risk is a difficult task to undertake since elderly patients (from developed countries) are likely to die either of cancer or of cardiovascular disease.”

Lars H Lindholm, Bo Carlberg
Lancet 2010

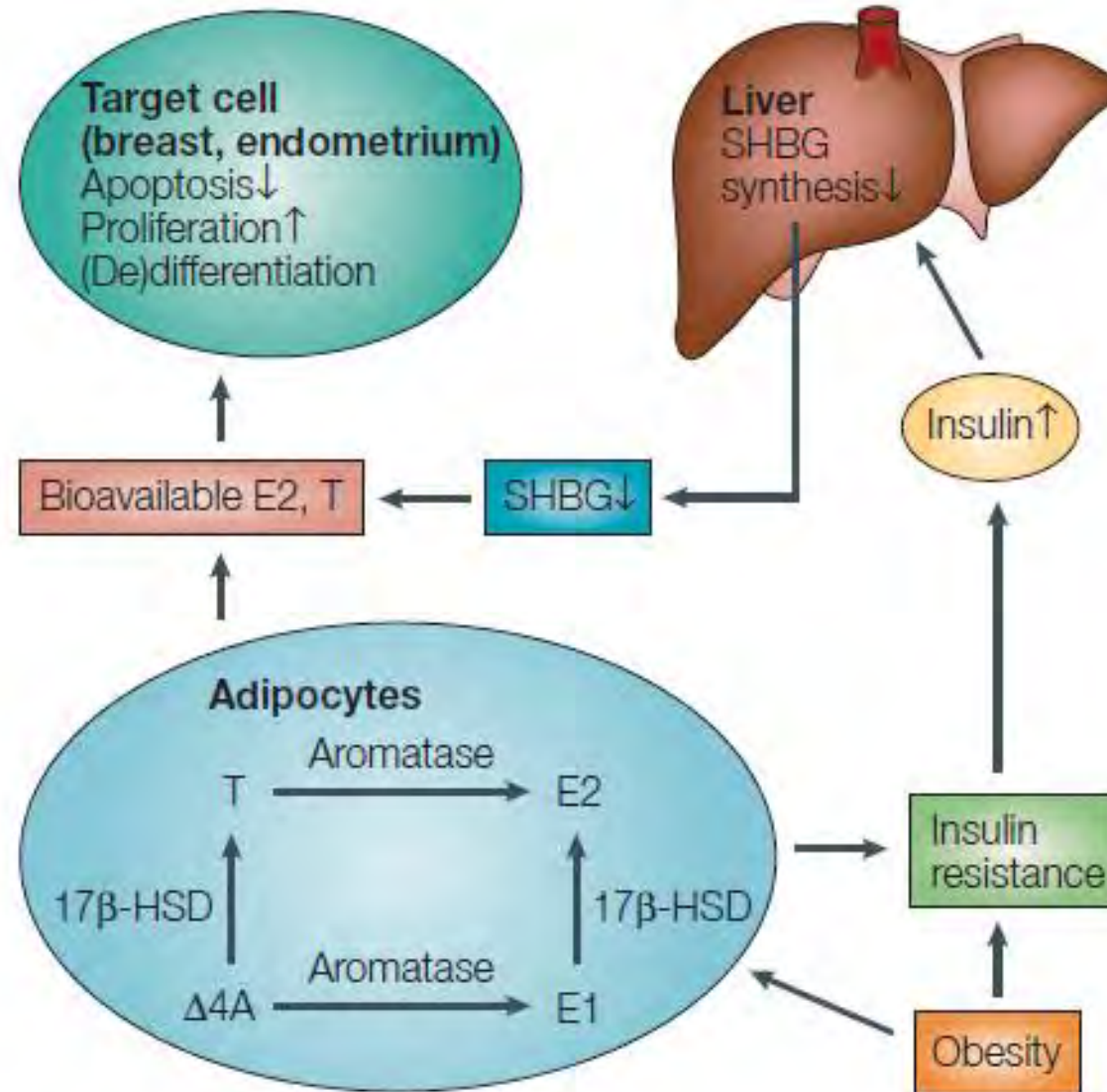
Obesity and risk of cancer: potential mechanisms (1)

Insulin resistance and its impact



Obesity and risk of cancer: potential mechanisms (2)

The hormonal pathways



Obesity-related cancers

Type of cancer	Relative risk* with BMI of 25–30 kg/m ²	Relative risk* with BMI of ≥ 30 kg/m ²	PAF (%) for US population [‡]	PAF (%) for EU population [§]
Colorectal (men)	1.5	2.0	35.4	27.5
Colorectal (women)	1.2	1.5	20.8	14.2
Female breast (postmenopausal)	1.3	1.5	22.6	16.7
Endometrial	2.0	3.5	56.8	45.2
Kidney (renal-cell)	1.5	2.5	42.5	31.1
Oesophageal (adenocarcinoma)	2.0	3.0	52.4	42.7
Pancreatic	1.3	1.7	26.9	19.3
Liver	ND	1.5–4.0	ND	ND
Gallbladder	1.5	2.0	35.5	27.1
Gastric cardia (adenocarcinoma)	1.5	2.0	35.5	27.1