Breast Cancer Prevention

Where do we go from here?

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Today's talk

- Endocrine agents for breast cancer prevention
- Biomarkers
- Current clinical trials

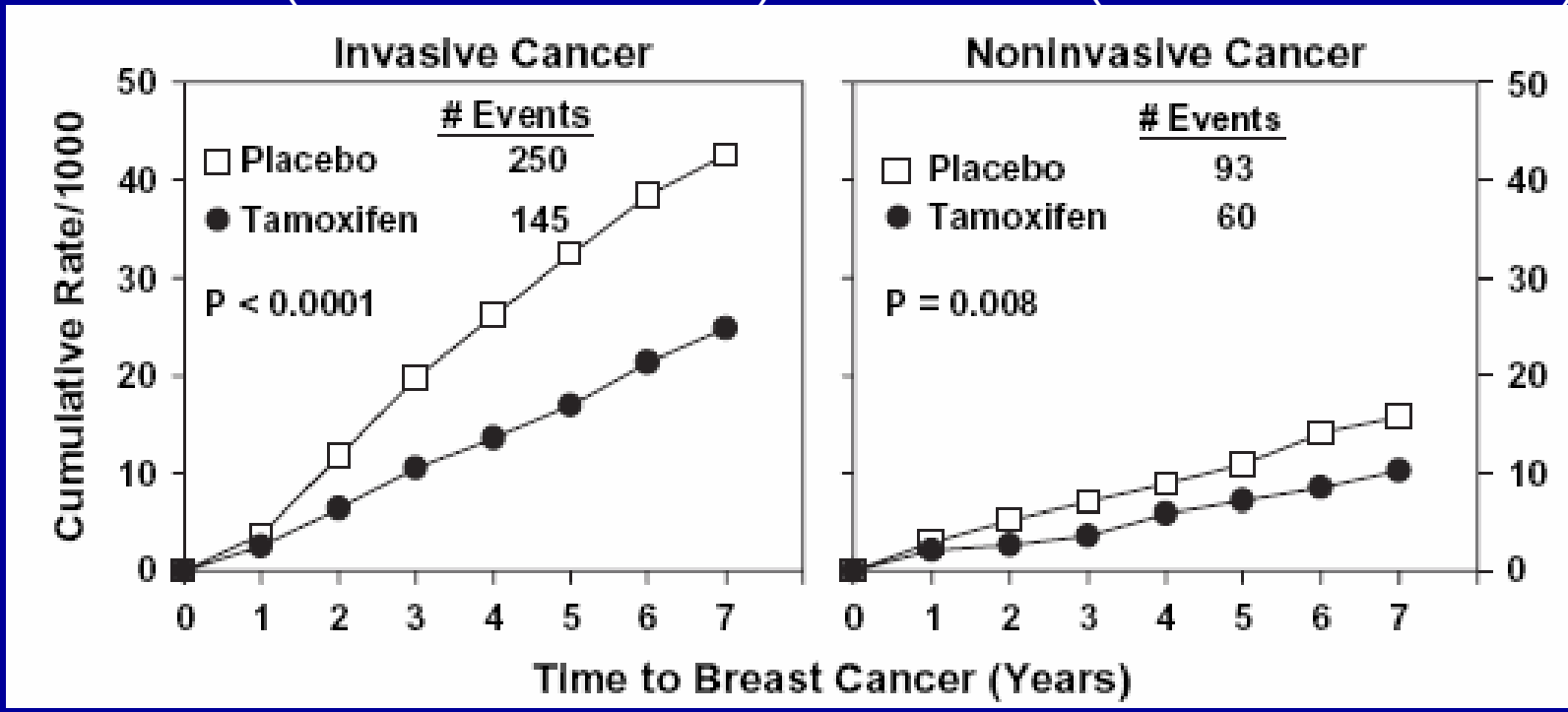
Proven agents for breast cancer prevention

- Selective estrogen receptor modulators
  - Tamoxifen
  - Raloxifene
- Aromatase Inhibitor
  - Exemestane
- Reduce the risk of developing invasive and non-invasive breast cancer
- Side effect profiles differ

NSABP-P1: Tamoxifen vs. placebo

RR = 0.57 (95% CI = 0.46 to 0.70)

RR = 0.63 (95% CI = 0.45 to 0.89)

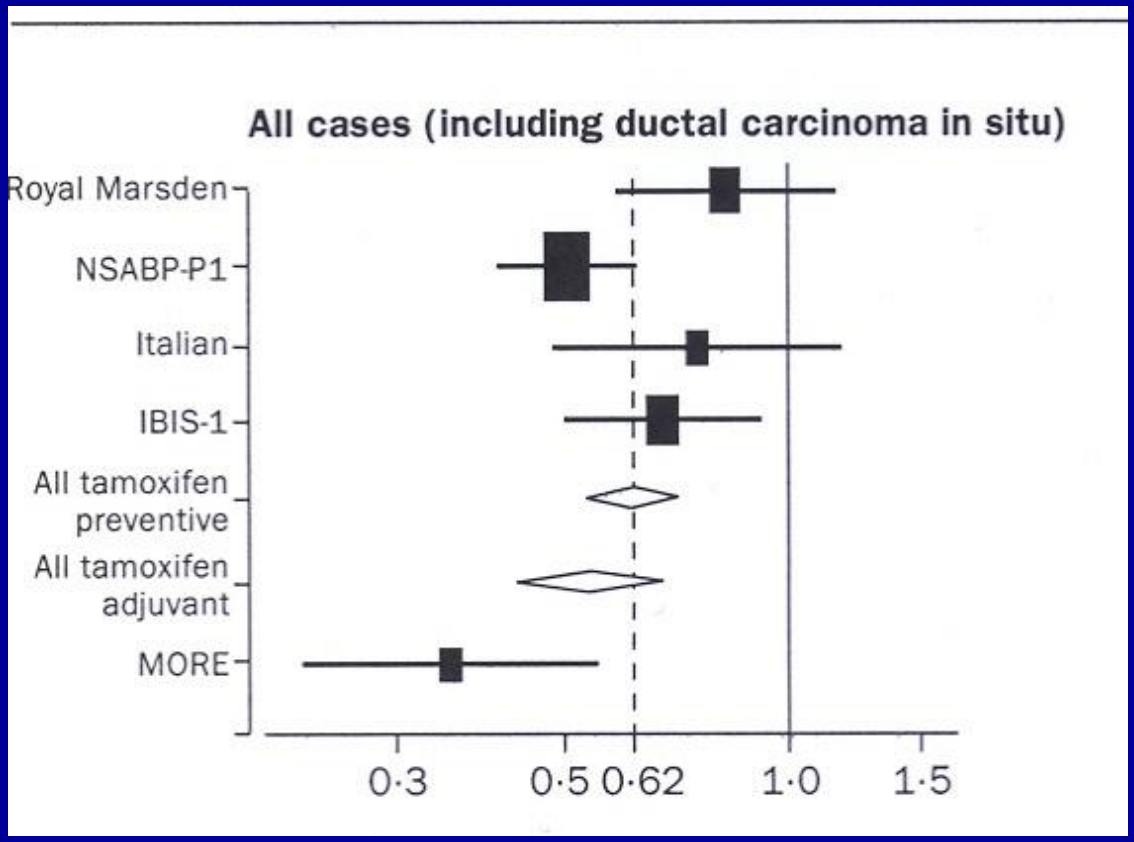


ER+ RR = 0.38 (0.28-0.50)

ER- RR = 1.31 (0.86-2.01)

Fisher, B et al., JNCI 2005, 97: 1652-1662

Tamoxifen Breast Cancer Prevention Studies



Cuzick et al, Lancet 2003

NSABP Protocol P-2

Risk eligible
postmenopausal women

Stratification for:
Relative risk
Age
Race
h/o LCIS

Tamoxifen
20 mg/day x 5 years
N=9726

Raloxifene
60 mg/day x 5 years
N=9745

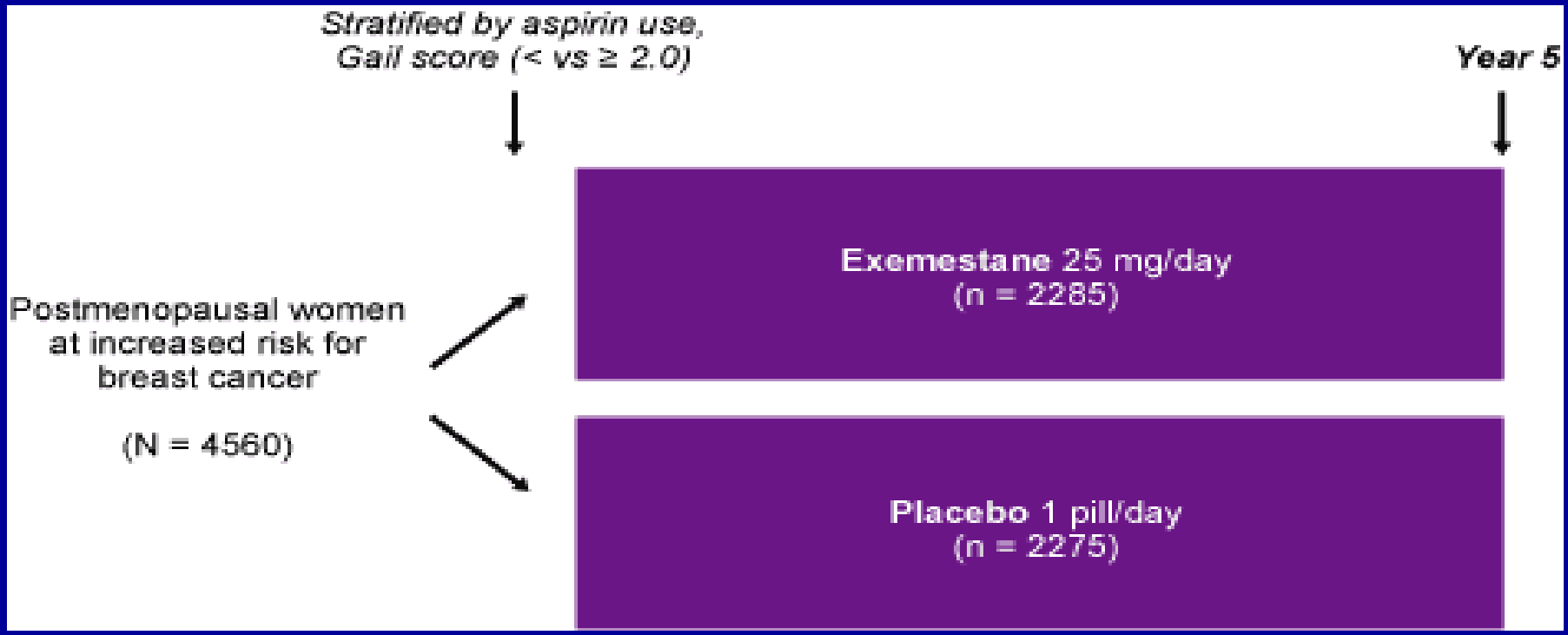
Events on Tamoxifen and Raloxifene in Women at risk for breast cancer

	Tamoxifen Annual event rate/1000	**Raloxifene** Annual event rate/1000	**Risk Ratio**	**95% CI**
Invasive breast cancer	4.04	5.02	1.24	1.05,1.47
Non-invasive breast cancer	1.83	2.23	1.22	0.95, 1.59
Thrombo-embolic events	1.93	1.38	0.72*	0.54, 0.95
Endometrial cancer	2.25	1.23	0.55*	0.36, 0.83
Stroke	1.39	1.33	0.96	0.64, 1.43
Cataracts	14.58	11.69	0.80*	0.72, 0.89
Osteoporotic fractures	2.73	2.51	0.92	0.69, 1.22

* Favors raloxifene

Vogel, V. G.et al. Cancer Prev Res 2010

NCIC MAP.3 Trial

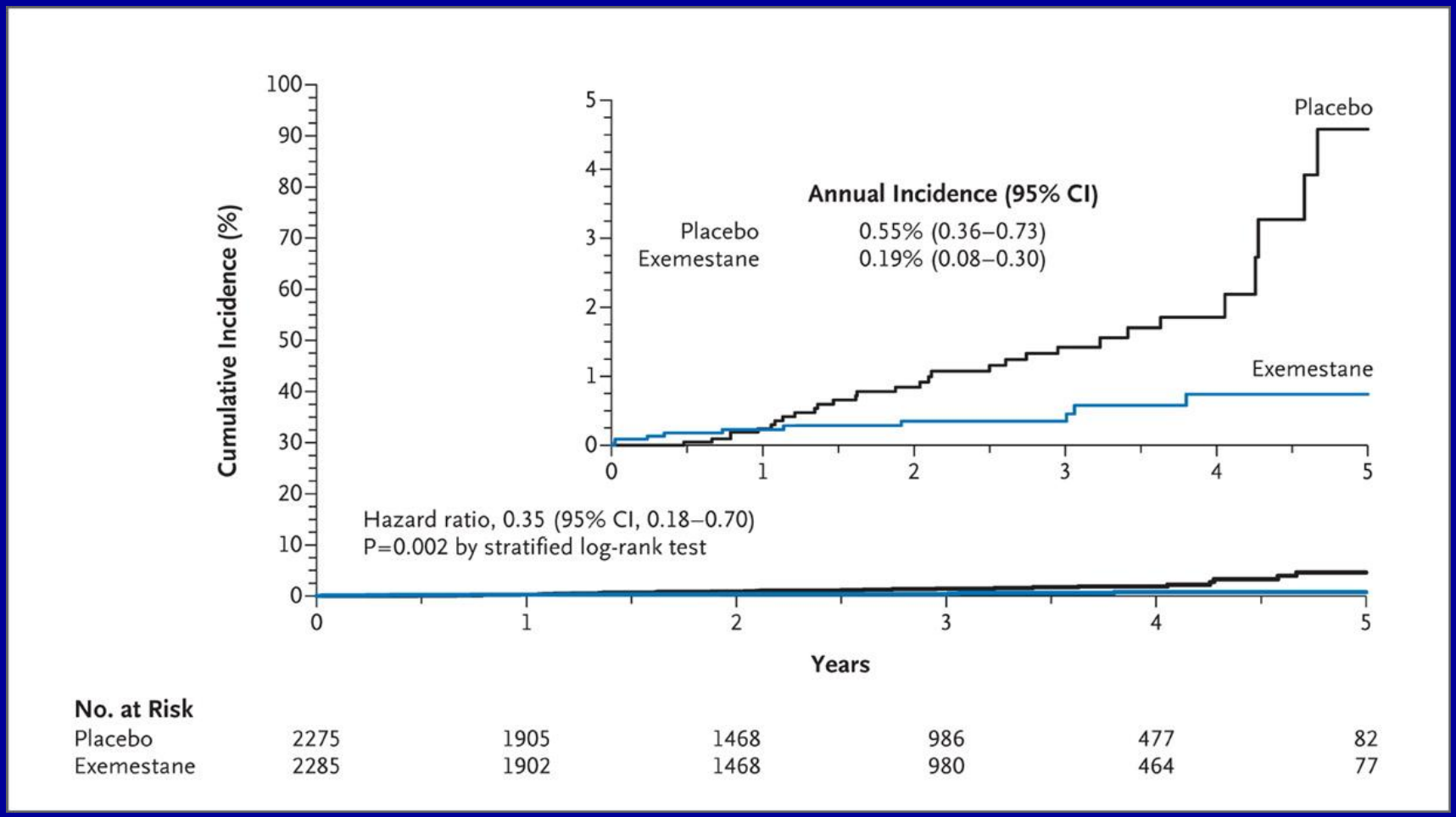


Eligibility:

- >60 yr old
- Gail model>1.66%
- Atypical hyperplasia
- LCIS
- DCIS s/p mastectomy

Goss et al NEJM June 2011

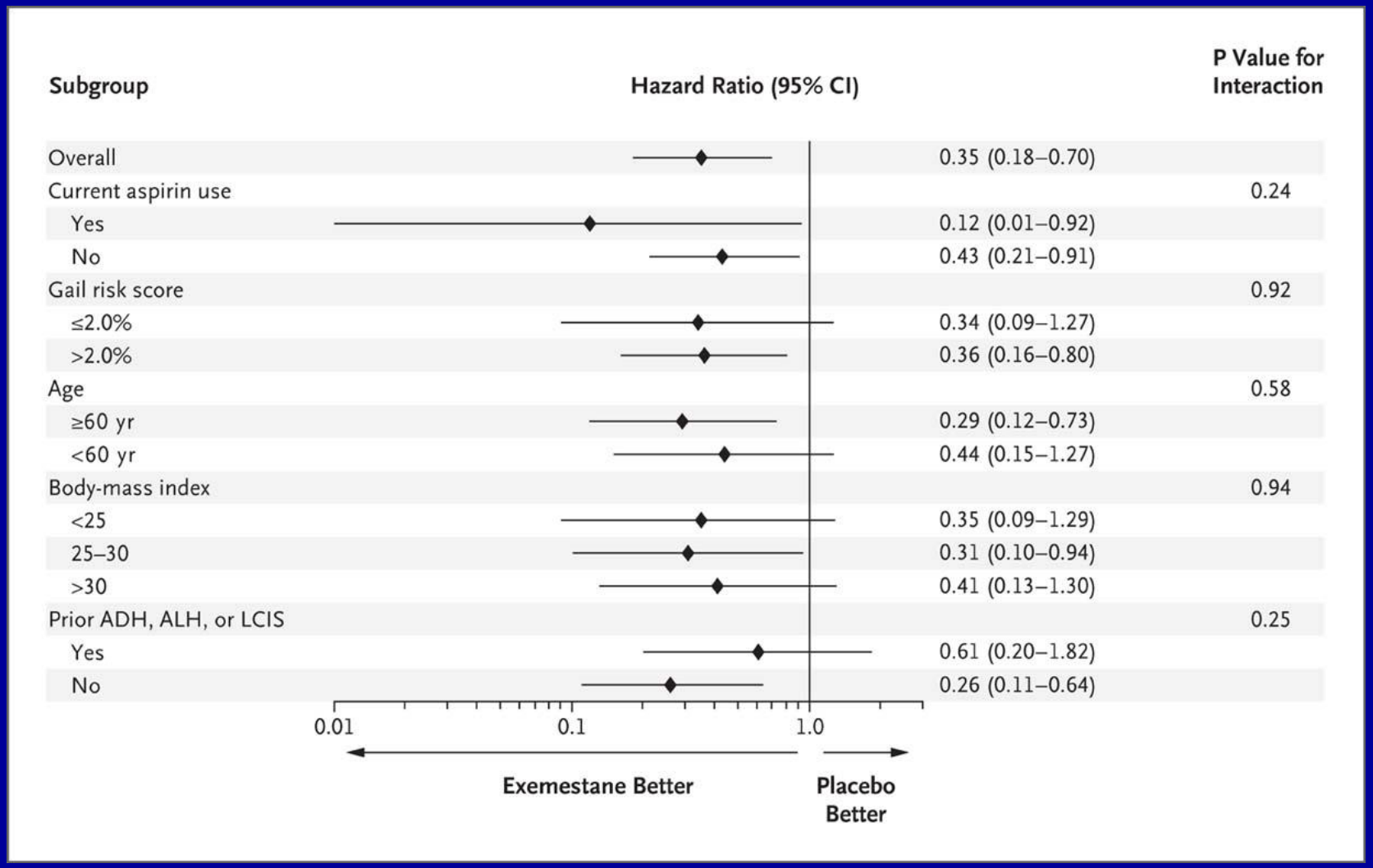
MAP.3 Results: Incidence of Invasive Breast Cancer



Goss PE et al. N Engl J Med 2011;364:2381-2391.

The NEW ENGLAND JOURNAL of MEDICINE

MAP.3 Results: Sub-group Analyses



Goss PE et al. N Engl J Med 2011;364:2381-2391

The NEW ENGLAND JOURNAL of MEDICINE

MAP 3 Results: Types of breast cancer

	exemestane	placebo	HR	P-value
Invasive breast cancer	11	32	0.35	0.002
ER+	7	27	0.27	0.001
ER-	4	5	0.80	0.74
DCIS	9	14	0.65	0.31

Goss et al NEJM June 2011

MAP.3 Results: Adverse Events (all grades)

	Exemestane %	Placebo %	P-value
Hot flashes	40	32	<0.001
Fatigue	23	21	0.03
Arthritis	11	9	0.01
Diarrhea	5	3	0.002
New osteoporosis	1.7	1.3	0.39
CV events	4.7	4.9	0.78
Fracture	6.7	6.4	0.72
QOL SF 36	NA	NA	0.91

Goss PE et al. N Engl J Med 2011;364:2381-2391

Summary Prevention Agents

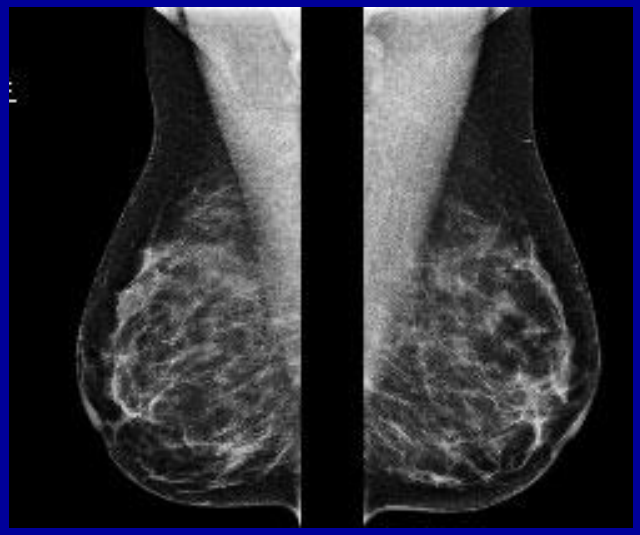
	Population	Efficacy	Usual side effects	Rare, serious side effects
tamoxifen	Pre Post	50% reduction	•Hot flashes •Vaginal discharge	•VTE •Endometrial cancer •cataracts
raloxifene	Post	38 % reduction	•MS complaints •Dyspareunia	•VTE •NO endometrial cancer
exemestane	Post	65% reduction	•Arthralgias •Decrease in BMD	•? CV events •? Fracture risk

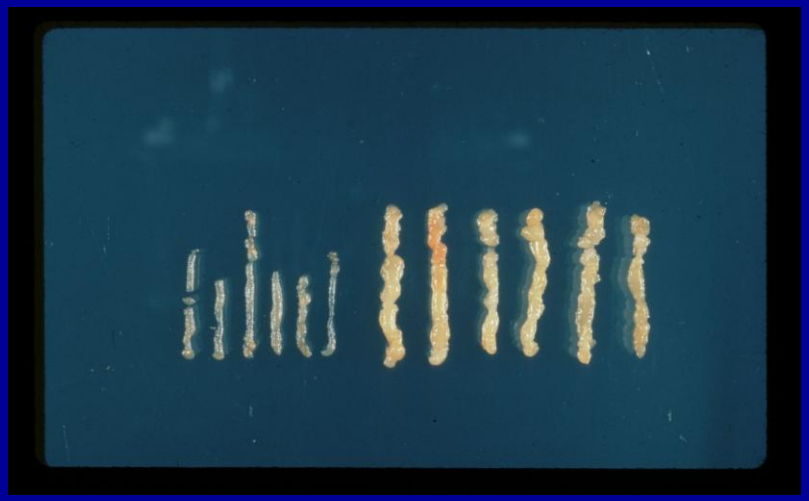
Current Breast Cancer Prevention

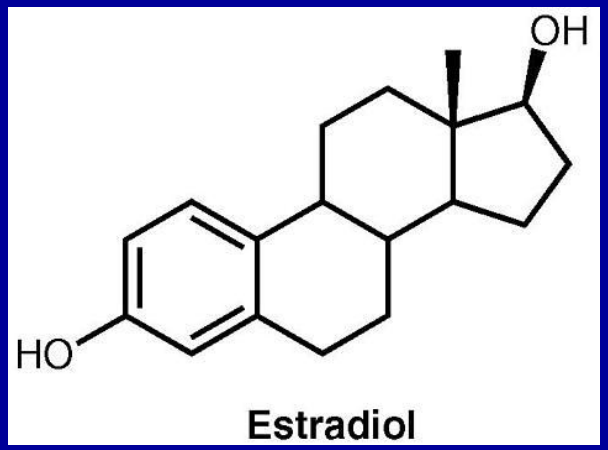
- Effective prevention agents for HR+ breast cancer
- Cost-effective
- Nobody uses
  - 2005: 0.08% (51,575) of women aged 40-79 took tamoxifen
- Trials comparing tamoxifen to AI in DCIS pending (IBIS-II, NSABP B-35)
- No large scale prevention trials on the horizon
- Need to identify promising agents

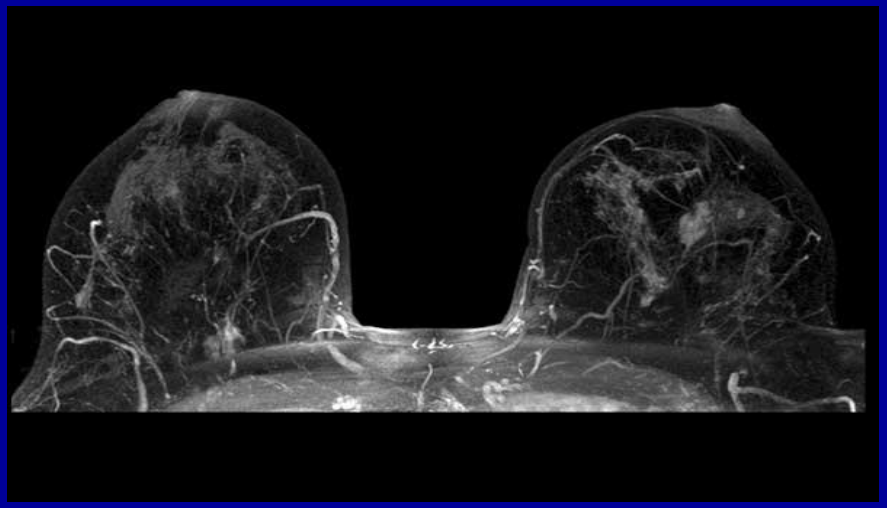
Noah-Venhoucke et al, Cancer 2011
Waters et al CEBP Feb 2010

Biomarkers









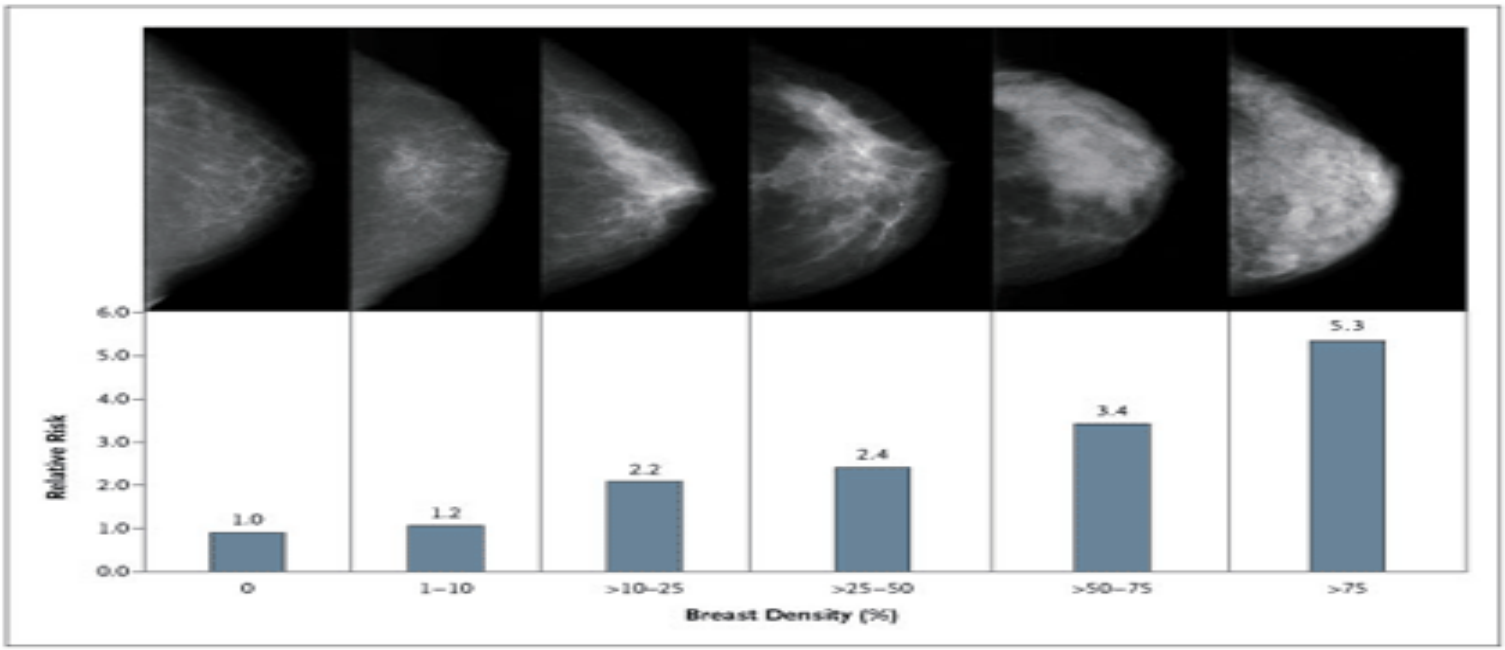
Biomarkers in Chemoprevention

Surrogate endpoint biomarkers

- Factors associated with breast cancer risk
  - Differential prevalence in high vs low risk groups
  - Reflect pathophysiology of breast carcinogenesis
- Modulated by agent
- Factors associated with safety (e.g. bone mineral density)
- Cost and time efficient
  - Ensure that most effective agents move forward in larger, costly studies
- Validation requires correlation with decreased cancer incidence in phase III studies

What is mammographic density?

- Fat is lucent
- All else is dense
  - Glandular tissue
  - Connective tissue (stroma)



Boyd, NEJM 2007

Mammographic Density (MD)

- Risk factor for breast cancer
  - odds ratio of approximately 4.0 or greater
- Increased MD correlates with risk for hormone receptor (HR) positive and HR negative breast cancer
- Important modifiers:
  - body mass index
  - menopausal status
  - age
  - exogenous endocrine agents (HRT, GnRh agonists, tamoxifen)

Cuzick et al, Br Can Res Tr 2008
Diorio et al, CEBP 2005

MD: validated surrogate biomarker

- IBIS -1 trial nested case control study (N=942)
  - Tamoxifen vs. placebo in prevention setting
- 46% of women on tamoxifen had a 10% or greater decrease in MD at 12-18 months
  - ≥10% decrease in MD had a 63% reduction (p=0.002) in breast cancer risk
  - <10% decrease no risk reduction (OR 1.13, p=0.6)
- Change in MD is useful predictor of response to tamoxifen

Interventions under study

- Metformin
- Vitamin D
- Soy
- Grapeseed extract
- Flaxseed lignans
- Omega 3 fatty acids
- Statins
- SERMS
  - Lasofoxifene
  - Low dose tamoxifen
- Lifestyle: diet and exercise interventions

Insulin and breast cancer

- DMII modest increased risk of breast cancer
- WHI : higher insulin and HOMA-1R increased risk for postmen breast ca
  - Independent of BMI and estradiol
  - HR for highest vs lowest quartile of insulin level = 1.46, 95% CI 1.00 to 2.13, P-trend = .02
- Early breast ca pts (pre and post, without DMII)
  - highest insulin levels are 2x more likely to have recurrence HR 2.0 (95% CI, 1.2 to 3.3)
  - 3x more likely to die of breast ca HR 3.1 (95% CI, 1.7 to 5.7)

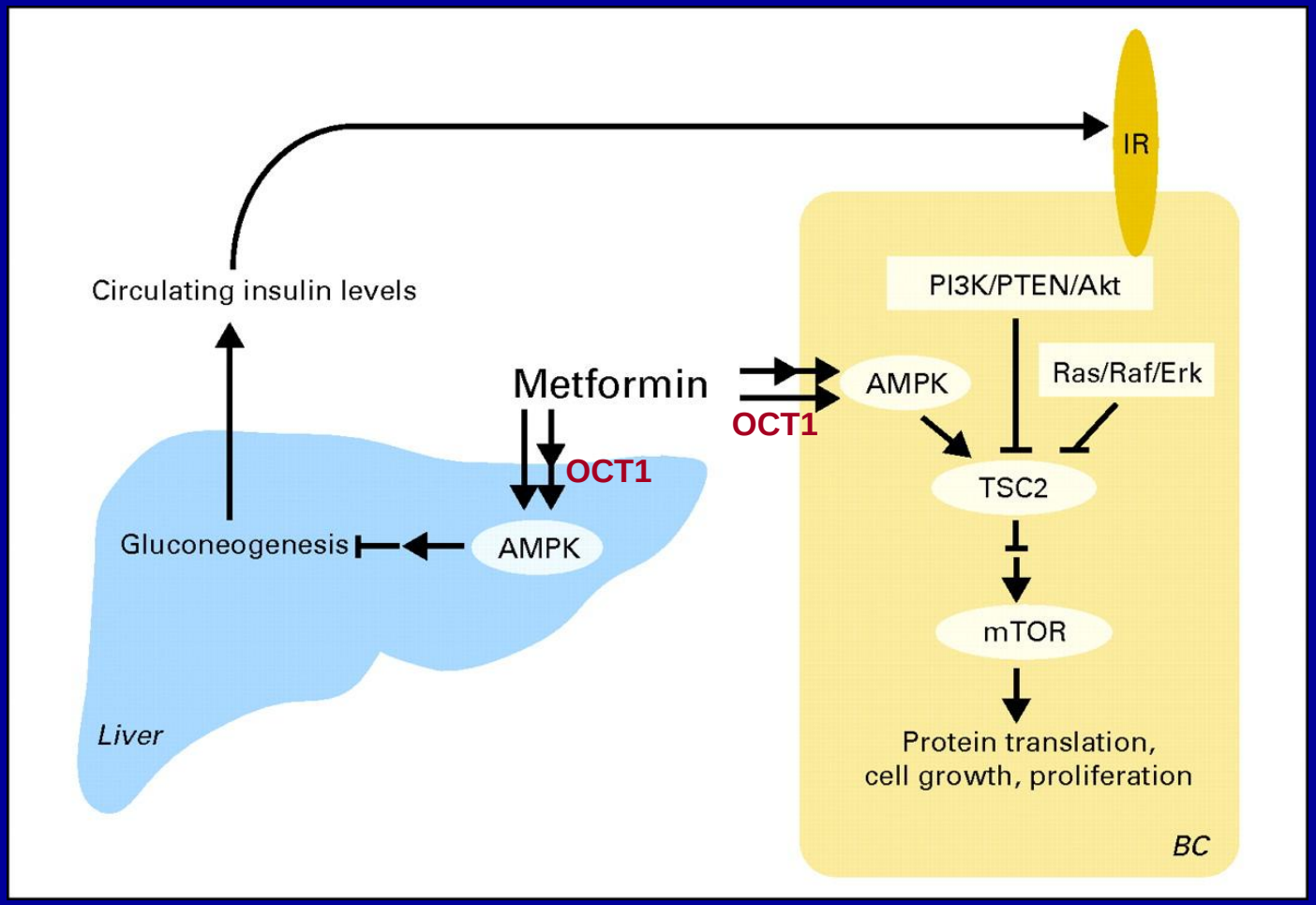
Wolf et al Lancet Oncol 2005
Gunter et al JNCI 2009
Goodwin et al JCO 2002

Metformin and breast cancer

- Improves path CR
  - Neoadjuvant treatment- women with DM on metformin (N=68) had 24% path CR versus 8% DM not on metformin (N=87)
- Safe in breast cancer patients w/o DMII
  - 1500 mg/day x 6 months, insulin decreased 22%
  - ?ultimate 4% improvement in DFS, OS

Jiralerspong et al JCO 2009
Goodwin et al Clin Breast Cancer 2008

Mechanism of Metformin Action

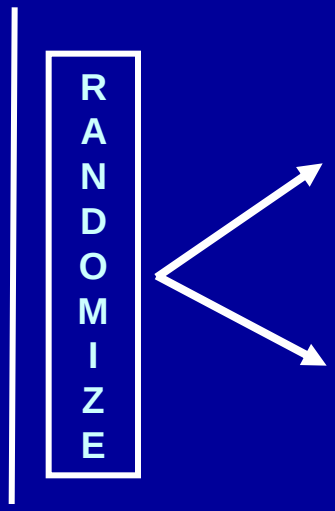


Goodwin P J et al. J Clin Oncol 2009; 27:3271-3273

NCIC CTG MA.32 STUDY SCHEMA

T1–3*, N0-3,M0 invasive breast cancer surgically removed within 1 year
Radiotherapy, chemotherapy, endocrine therapy, trastuzumab, biologics, bisphosphonates**

*** If pT1C, ≥ 1 adverse prognostic factor**
**** CXT must be completed**

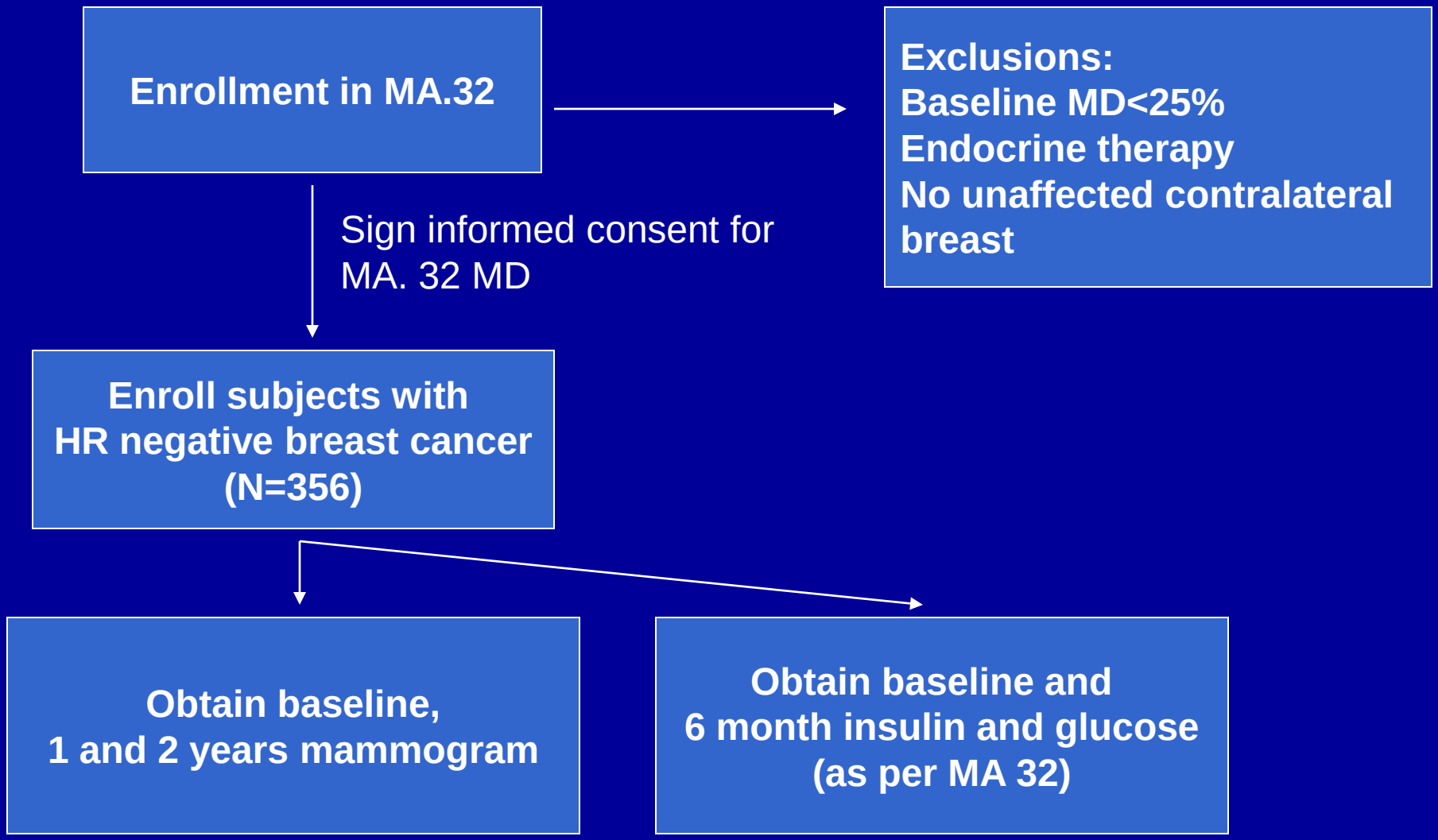


Metformin
850 mg po bid X 5 years
(includes 4-week ramp-up of 850mg po daily)

Identical Placebo
One caplet po bid X 5 years
(includes 4 week ramp-up of one caplet po daily)

Primary Outcome:	**Invasive cancer free survival**

MA. 32 Mammographic Density Study



PI: J. Eng-Wong, I. Mayer

MA.32 MD Study Endpoints

- Primary endpoint:
  - Determine the change MD in contralateral breast from prior to the initiation of metformin or placebo through one year of therapy in subjects with hormone receptor negative breast cancer (i.e. not on endocrine therapy)

- Secondary endpoints:
  - To correlate baseline MD with baseline fasting plasma insulin and glucose levels.
  - Determine if MD change correlates with changes in fasting plasma insulin and glucose levels over the same time period
  - Evaluate MD change after 2 years of intervention

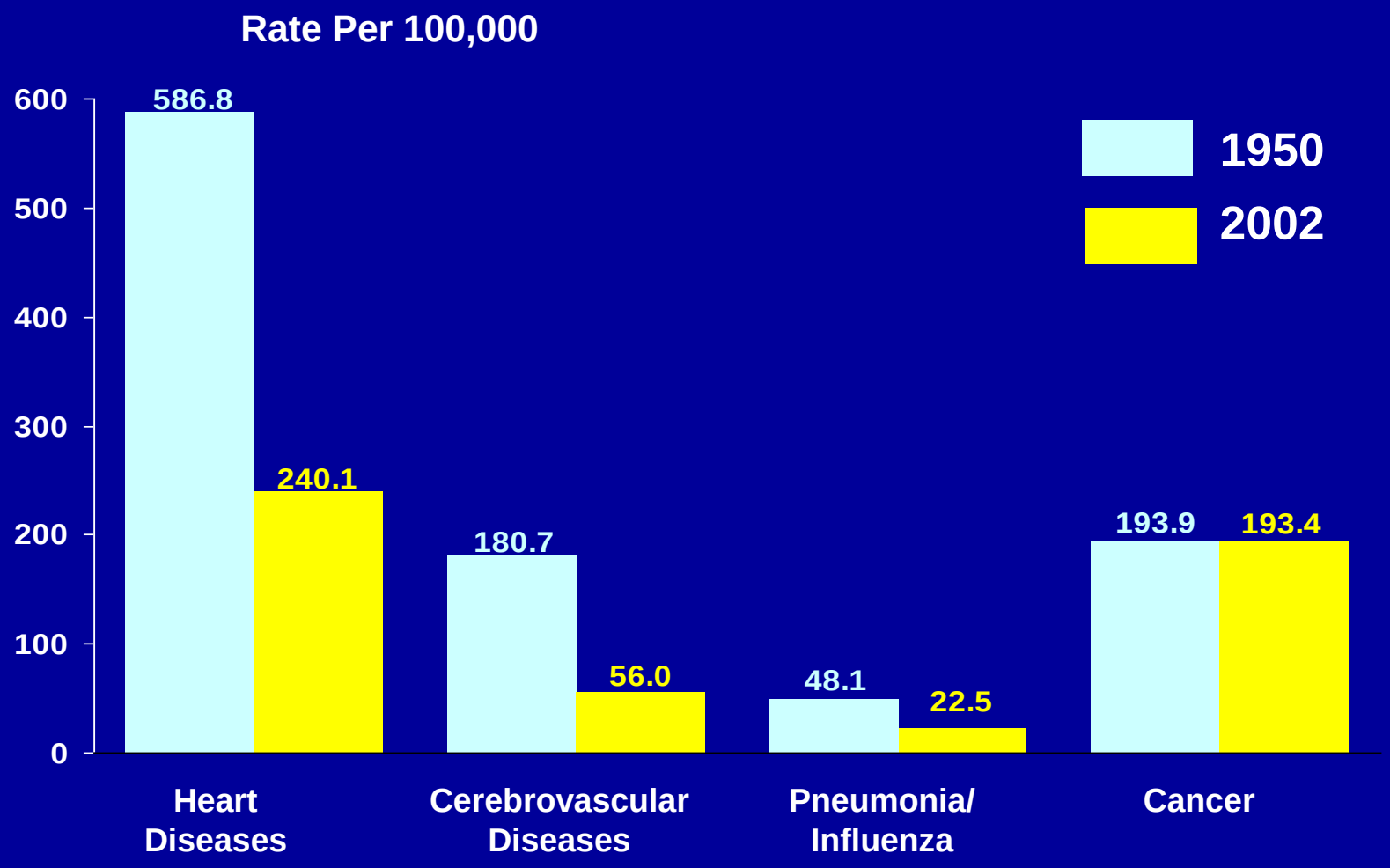
Summary

- Useful prevention agents for hormone receptor positive breast cancer are available and underutilized
- Promising work in identifying biomarkers of efficacy
- Validation studies key

Future Directions

- How do we improve uptake of already approve agents?
- What is the best dosing/duration of current agents?
- What will prevent hormone receptor negative breast cancer?
- Are current agents effective in BRCA ½ mutation carriers?
- What are the appropriate biomarker endpoints and what is good enough to warrant a large phase III trial?

Change in the US Death Rates* by Cause, 1950 & 2002



* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.
2002 Mortality Data: US Mortality Public Use Data Tape, 2002, NCHS, Centers for Disease Control and Prevention, 2004

Metformin Activity Across Molecular Subtypes of Breast Cancer (Cell Lines in vitro)

Molecular Subtype	Proliferation	Colony Formation	Cell Cycle	Apoptosis	Molecular Changes			
					AMPK/ AKT	mTOR	erbB2	Other
Luminal A	↓	↓	G_1 arrest (partial)	No	↓	↓	–	↓ cyclin D_1, E2F-1
Luminal B	↓	↓	G_1 arrest (partial)	No	↓	↓	–	↓ cyclin D1, E2F-1
HER2	↓	↓	G_1 arrest (partial)	No	↓	↓	- ↓ expression (high dose) - ↓ Tk activity (low dose)	↓ cyclin D1, E2F-1
Triple Negative	↓	↓	G_1 arrest (partial) S phase arrest (partial)	Yes*	↓		–	- ↓ cyclin D1, E - inactivation of EGFR and downstream signaling - ↓ TN xenograft growth in nude mice

***** Via (1) PARP cleavage
(2) activation of intrinsic (mitochondrial integrity, caspase-9) and extrinsic (cell surface death receptors, caspase-8) pathways

Alimova IN et al. *Cell Cycle 2009; 8:909-915*
Liu B et al. *Cell Cycle 2009; 8:1-10*

Benefit/risk indices for tamoxifen and raloxifene chemoprevention by level of 5-year projected risk for invasive breast cancer (IBC) for white non-Hispanic women with a uterus, by age group.

5-Year Projected Risk of IBC (%)	Tamoxifen *v* Placebo (with uterus)			Raloxifene *v* Placebo (with uterus)		
	50-59	60-69	70-79	50-59	60-69	70-79
1.5	-133	-310	-325	21	-11	-15
2.0	-105	-283	-298	43	11	7
2.5	-78	-255	-271	65	33	29
3.0	-51	-228	-244	86	55	51
3.5	-25	-202	-217	108	76	71
4.0	3	-175	-190	128	97	93
4.5	29	-148	-164	150	119	115
5.0	56	-121	-137	172	140	136
5.5	83	-95	-111	193	161	157
6.0	109	-69	-84	214	183	179
6.5	135	-42	-58	236	204	199
7.0	162	-15	-32	256	225	221

- Strong evidence of benefits outweighing risks
- Moderate evidence of benefits outweighing risks
- Benefits do not outweigh risks

5-year projected risk of IBC is ≥ 1.67%.

Using BCPT data and WHI baseline rates

Combining RR from BCPT and STAR using WHI baseline rates

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MAP.3 Participants

	Exemestane (N=2285)	Placebo (N=2275)
White race	93.6	93.3
Median age	62.5	62.4
High risk by (%):		
Gail Model	40.7 (score 2.3)	39.8 (score 2.3)
Age ≥60	48.8	49.5
AH, LCIS	8.1	8.3
DCIS s/p MRM	2.5	2.5