Exemestane: Keeping abreast of chemoprevention

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SEMINAR

OCTOBER 24TH, 2013

Background

- Breast cancer (CA)
  - most frequently diagnosed CA in Canadian ♀ > 20 yo
    - 2nd leading cause of CA death (after lung CA)
    - 1 in 9 expected to develop breast CA by 90 yo

New breast cancer cases diagnosed in Canadian women	**2013 (#)**
Annually	23,800
Weekly (average)	456
Daily (average)	65

Canadian Cancer Society's Advisory Committee on Cancer Statistics. Canadian Cancer Statistics 2013. Toronto, ON: Canadian Cancer Society; 2013

Background

Five-year relative survival rates for breast cancer by age group (men and women)						
All	15 – 39	40 – 49	50 – 59	60 – 69	70 – 79	80 – 99
88%	85%	90%	89%	90%	88%	80%

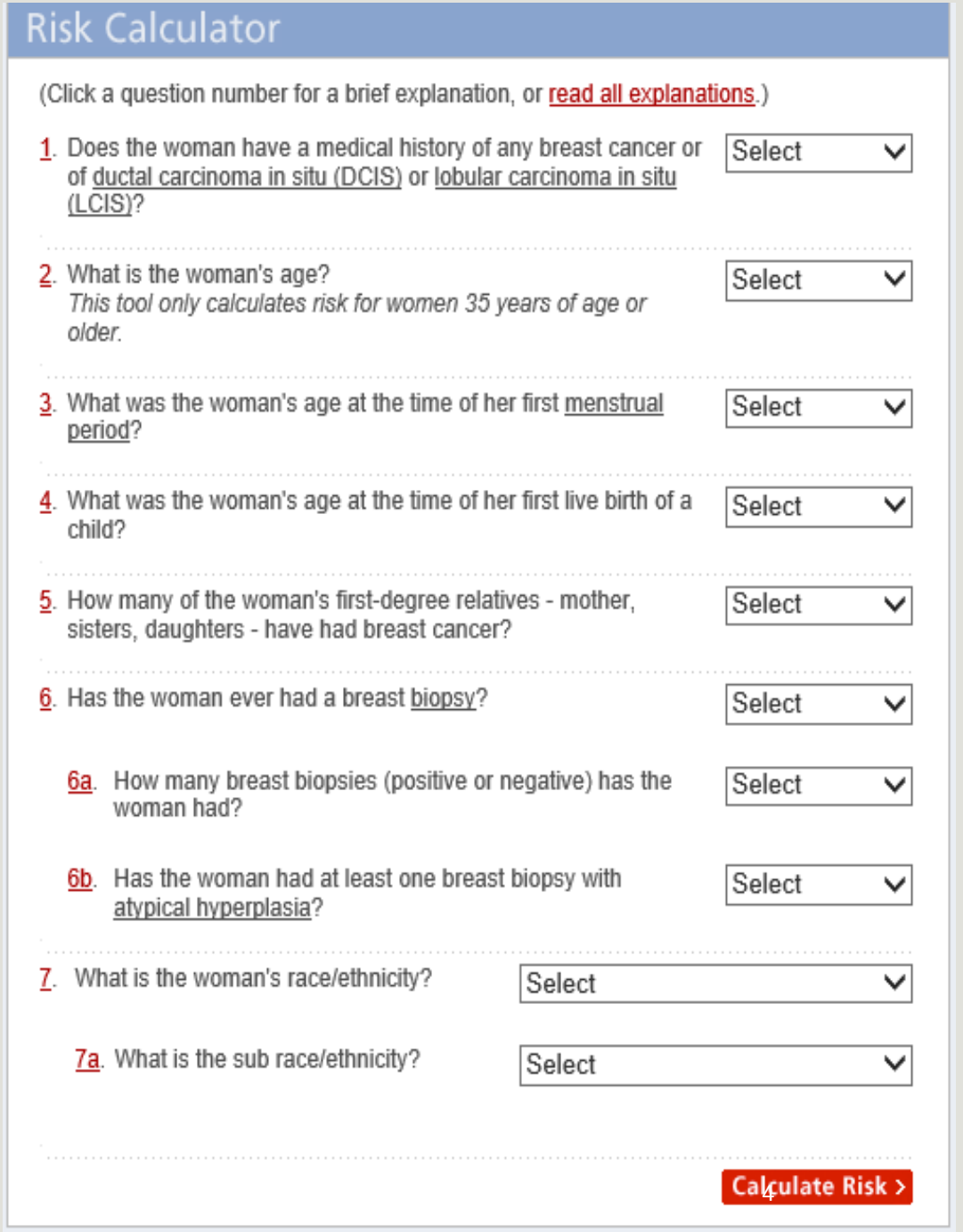
- Endogenous and exogenous estrogens
  - Significant role in breast cancer development
  - Risk factors for breast CA
    - *Linked to timing of exposure* and *cumulative exposure*

Canadian Cancer Society's Advisory. Committee on Cancer Statistics. Canadian Cancer Statistics 2013. Toronto, ON: Canadian Cancer Society 2013
CMAJ 2001, 12;164(12):1681-90

Assessing Risk

- **Gail Model**
- Data from NCI and Breast Cancer Detection Demonstration Project (BCDDP): >280,000 women 35-74 yo
- High risk: >1.66% 5 yr risk
- **Limitations**

http://www.cancer.gov/bcrisktool/about-tool.aspx#gail

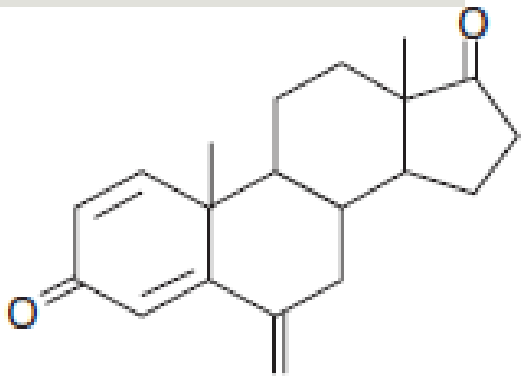


Case - AJ

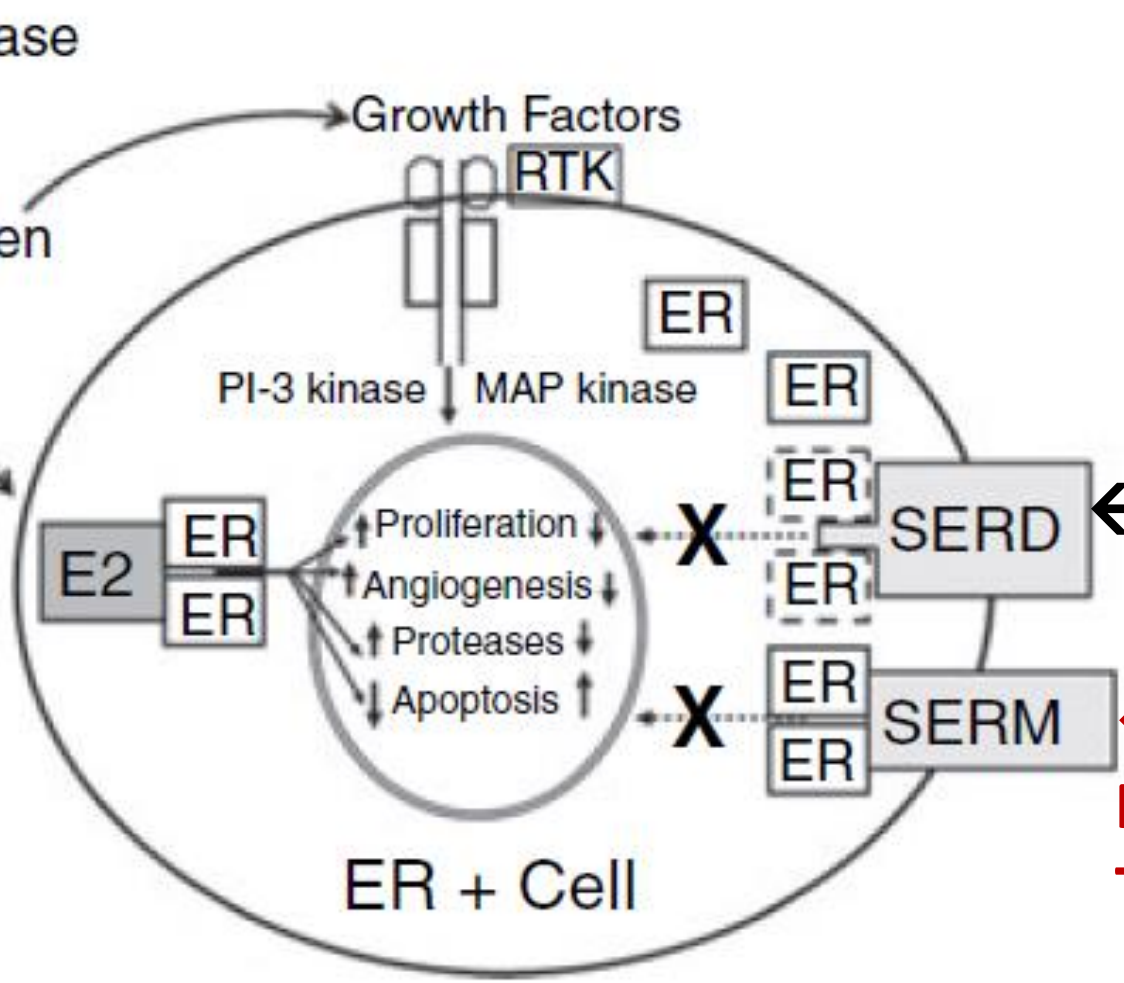
- 38 yo ♀ actress
- Married, 6 children (3 adopted)
- No medical conditions, nonsmoker
- Mother → breast CA, died from ovarian CA at 56 yo
  - Aunt → died from breast CA at 61 yo
- BRCA1 mutation carrier (so was her aunt)
- GAIL model: 5 yr risk=1.3%, lifetime risk=27.1%
- She inquires about **oral agents** to reduce risk of breast cancer
  - Who would offer???: 1. Tamoxifen 2. Raloxifene 3. Exemestane 4. Nothing

Potential Targets for Chemoprevention

EXEMESTANE
LETROZOLE → AI
ANASTROZOLE



Exemestane



←FULVESTRANT

←

RALOXIFENE
TAMOXIFEN

Fabian CJ. Int J Clinical Practice 2007

Oral Agents for Chemoprevention

AGENT	INDICATIONS
TAMOXIFEN (SERM)	• Adjuvant tx breast CA • Tx metastatic breast CA • ↓risk of invasive BC in pre/postmenopausal ♀ with DCIS or high risk (FDA)
RALOXIFENE (SERM)	• Tx & px of osteoporosis in postmenopausal ♀ • ↓risk of invasive BC in postmenopausal ♀ with osteoporosis and/or at high risk (FDA)
EXEMESTANE (Aromatase Inhibitor)	• Sequential adjuvant tx of postmenopausal ♀ with ER+ early BC after 2-3yrs tamoxifen • Tx of ER+ advanced BC in postmenopausal ♀ who have progressed after tamoxifen

Oral Agents for Chemoprevention

Agent	Trial Data	Efficacy Outcomes (RR of Invasive Breast Cancer)	Safety Outcomes (Adverse Events)
TAMOXIFEN (SERM)	**VS placebo:**		
	IBIS-I	0.73 (0.58-0.91)	↑ VTE, stroke
	Italian	0.87 (0.63-2.14)	↑ endometrial CA
	NSABP-1	0.54 (0.39-0.66)	↑ hot flashes, leg cramps
	Royal Marsden	0.94 (0.59-1.43)	↑ cataracts
	VS raloxifene:		↓ risk of vertebra #
	STAR	1.24 (1.05-1.47) * favoring tamoxifen	
RALOXIFENE (SERM)	**VS placebo:**		
	MORE	0.24(0.13-0.44)	↑ VTE, stroke
	CORE	0.41 (0.24-0.71)	↑ hot flashes, leg cramps
	RUTH	0.56 (0.38-0.83)	↓ risk of vertebral #
	VS tamoxifen:		No ↑ in endometrial CA
	STAR	1.24 (1.05-1.47)	

Guidelines – Recommendations

2001 Canadian Task Force on Preventive Health Care

- Gail model 5 yr risk ≥ 1.66%
  - Counsel on potential benefits and risks of tamoxifen (grade B)

2010 NCCN Guidelines on Breast Cancer Risk Reduction

- Consider tamoxifen or raloxifene - 5 yr breast CA risk 1.7% and life expectancy 10 yr
  - Aromatase inhibitor use - inappropriate unless part of clinical trial

2013 American Society of Clinical Oncology

- Discuss tamoxifen or raloxifene as options in premenopausal or postmenopausal ♀ >35 yo at increased risk or LCIS

CMAJ 2001; 164(12):1681-90
J Natl Compr Canc Netw 2010; 8:1112-1146
J Clin Oncol 2013, 31.

Guidelines

"Moderate, evidence based recommendation"

Agent	Old Recommendations (2009)[a]	New Recommendations[b]
Exemestane[i]	Use [of aromatase inhibitors] **is not recommended outside of the clinical trial setting to lower BC risk.**	*Should be discussed as an alternative to tamoxifen and/or raloxifene to reduce the risk of invasive BC, specifically ER-positive BC, in postmenopausal women age ≥ 35 years with a 5-year projected absolute BC risk ≥ 1.66%[e] or with LCIS or atypical hyperplasia.[ef]* *Should not be used for BC risk reduction in premenopausal women.* *Discussions with patients and health care providers should include both the risks and benefits of exemestane in the preventive setting.[g]* *Dosage: 25 mg per day orally for 5 years.*

Visvanathan et al. ASCO Clinical Practice Guideline J Clin Onc 2013;13.

Clinical Question

P: In postmenopausal women without pre-existing breast cancer, does

I: exemestane compared to

C: placebo or tamoxifen or raloxifene reduce the risk of

O: invasive breast cancer without significantly increasing risk of adverse effects or decreasing quality of life

Search Strategy

DATABASES	PubMed, EMBASE, IPA, Cochrane, Google Scholar
SEARCH TERMS	“exemestane” “raloxifene” “tamoxifen” “breast neoplasm”, “breast cancer” “prevention and control” “cancer prevention” “chemoprophylaxis” “chemoprevention”
LIMITS	English, humans
RESULTS	No comparative trials Lots of reviews!!!! **1 RCT- exemestane vs placebo**

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 23, 2011 VOL. 364 NO. 25

Exemestane for Breast-Cancer Prevention in Postmenopausal Women

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MAP.3 Study

Design	R, DB, PC, international (Canada, USA, Spain, France)
Population	**n=4560 postmenopausal ♀≥35 yo** **≥ 1 risk factor: ≥60 yo, Gail score >1.66%, prior atypical ductal, lobular hyperplasia, LCIS, or DCIS with mastectomy** • Exclusion: prior invasive BC, DCIS with lumpectomy, carriers of BRCA1 or BRCA2 genes, hx of malignancy, uncontrolled thyroid disease, chronic liver disease

MAP.3 Study

Intervention	Stratified by aspirin use (≤ 100mg/d) and Gail score (>2.0% and <2.0%) **Randomized:** 1. Exemestane 25 mg po daily + placebo 2. Exemestane 25 mg po daily + celecoxib 400 mg/d 3. Placebo + placebo Modified design: **1:1 ratio exemestane 25 mg po daily vs placebo**

MAP.3 Study

Outcomes	**Primary:** • **Incidence of invasive breast cancer** **Secondary:** • Combined incidence of invasive + non-invasive BC, ER- BC, atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, # breast biopsies, clinical fractures, adverse CV events, incidence of other cancers, **side effect profile and safety, health-related (SF36) and menopause-specific QOL (MENQOL)**
Follow-up	Event driven, planned max 5yrs or until a breast event, neoplastic dx, CV event or unacceptable toxicity →Clinical assessments at 6, 12 mos then q1yr (PE, breast exam, QOL) →Mammography q12 mos

MAP.3 – Statistical Analysis

- **Stratified log-rank test**
  - Compare time-to-event for primary and secondary endpoints
- **Cox proportional-hazards models**
  - Hazard ratios
- **Fisher's exact test**
  - Compare adverse events between groups
- **Chi-square test**
  - Compare differences in proportions of patients found to have a clinically meaningful changes in QOL

PATIENT CHARACTERISTICS

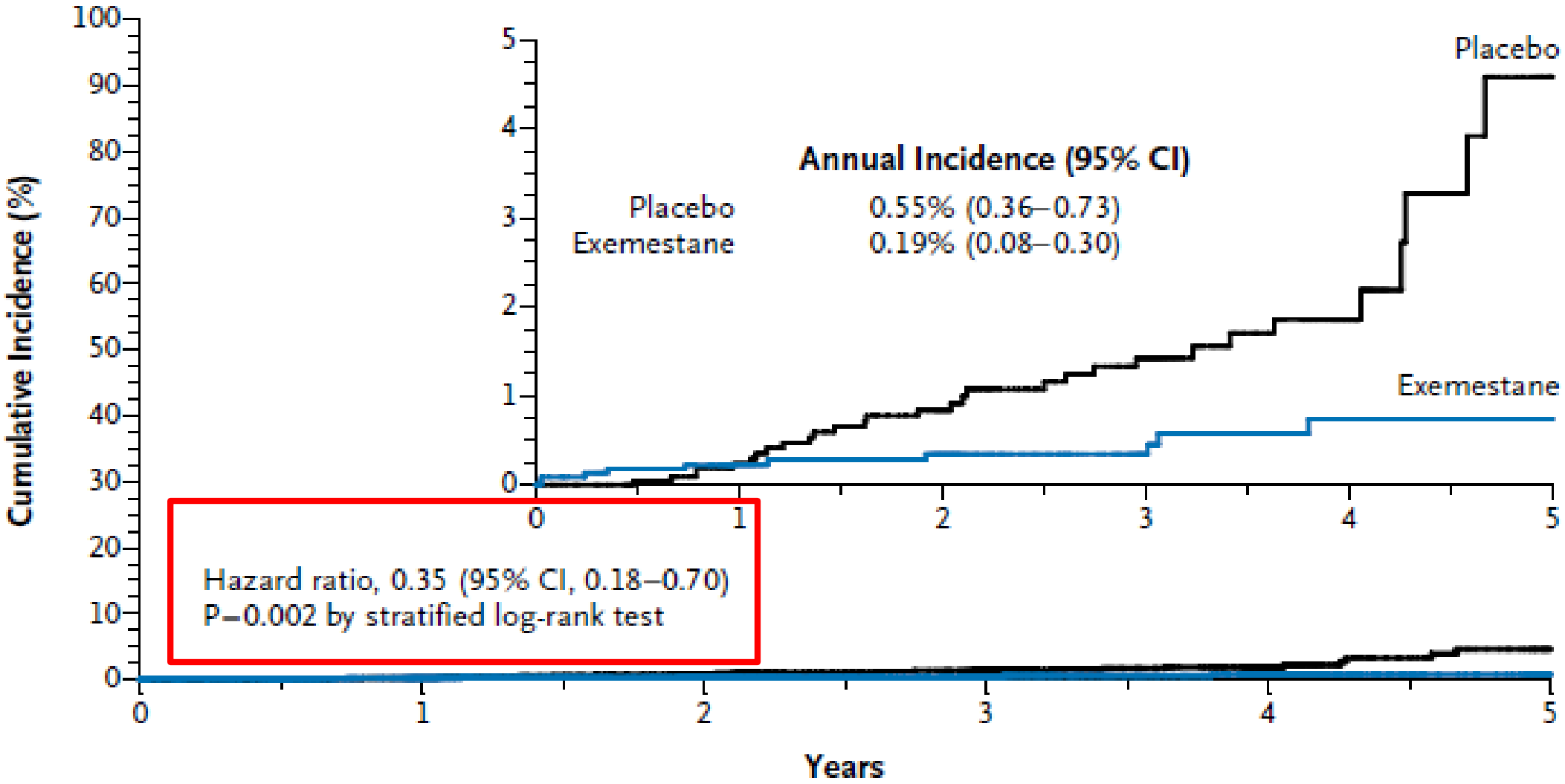
Table 1. Baseline Characteristics of Patients Randomly Assigned to Exemestane or Placebo.*

Characteristic	Exemestane (N=2285)	Placebo (N=2275)
White race — no. of patients (%)†	2138 (93.6)	2123 (93.3)
Age		
Median — yr	62.5	62.4
Range — yr	38.5–88.2	37.1–89.9
≥60 yr — no. of patients (%)	1545 (67.6)	1572 (69.1)
Body-mass index‡		
Median	27.9	28.1
Range	15.9–54.3	16.3–65.4
Breast cancer risk factors — no. of patients (%)		
Gail score indicating 5-year risk >1.66%§	929 (40.7)	905 (39.8)
Age ≥60 yr	1114 (48.8)	1126 (49.5)
Prior ADH, ALH, or LCIS on breast biopsy	185 (8.1)	188 (8.3)
Prior DCIS treated with mastectomy	56 (2.5)	56 (2.5)
Gail 5-yr risk score§		
No. of patients assessed	2171	2163
Median score — %	2.3	2.3
Range	0.6–21.0	0.6–15.1
Score >2.0 — no. of patients (%)	1321 (57.8)	1300 (57.1)
Prior therapy — no. of patients (%)		
Hormone-replacement therapy	1310 (57.3)	1327 (58.3)
Bisphosphonate therapy	427 (18.7)	414 (18.2)
Lipid-lowering drugs	738 (32.3)	696 (30.6)
Cardiovascular drugs	955 (41.8)	973 (42.8)
Selective estrogen-receptor modulators	104 (4.6)	116 (5.1)
Medical conditions — no. of patients (%)		
Prior clinical skeletal fracture	409 (17.9)	400 (17.6)
Current osteoporosis	303 (13.3)	293 (12.9)
Prior cardiovascular event	267 (11.7)	255 (11.2)

MAP.3 – Results

EVENTS	EXEMESTANE (n=2285)		PLACEBO (n=2275)		HR (95% CI)	P value
Invasive Breast Cancer						
	# Cases	Annual incidence %	# Cases	Annual Incidence %		
All cases	11	0.19	32	0.55	0.35 (0.18-0.70)	0.002
ER+	7	0.12	27	0.46	0.27 (0.12-0.60)	<0.001
ER-	4	0.07	5	0.09	0.80 (0.21-2.98)	0.74

Median of **35 months** follow-up (range 0-63.4)



No. at Risk						
Placebo	2275	1905	1468	986	477	82
Exemestane	2285	1902	1468	980	464	77

Figure 1. Cumulative Incidence of Invasive Breast Cancer.

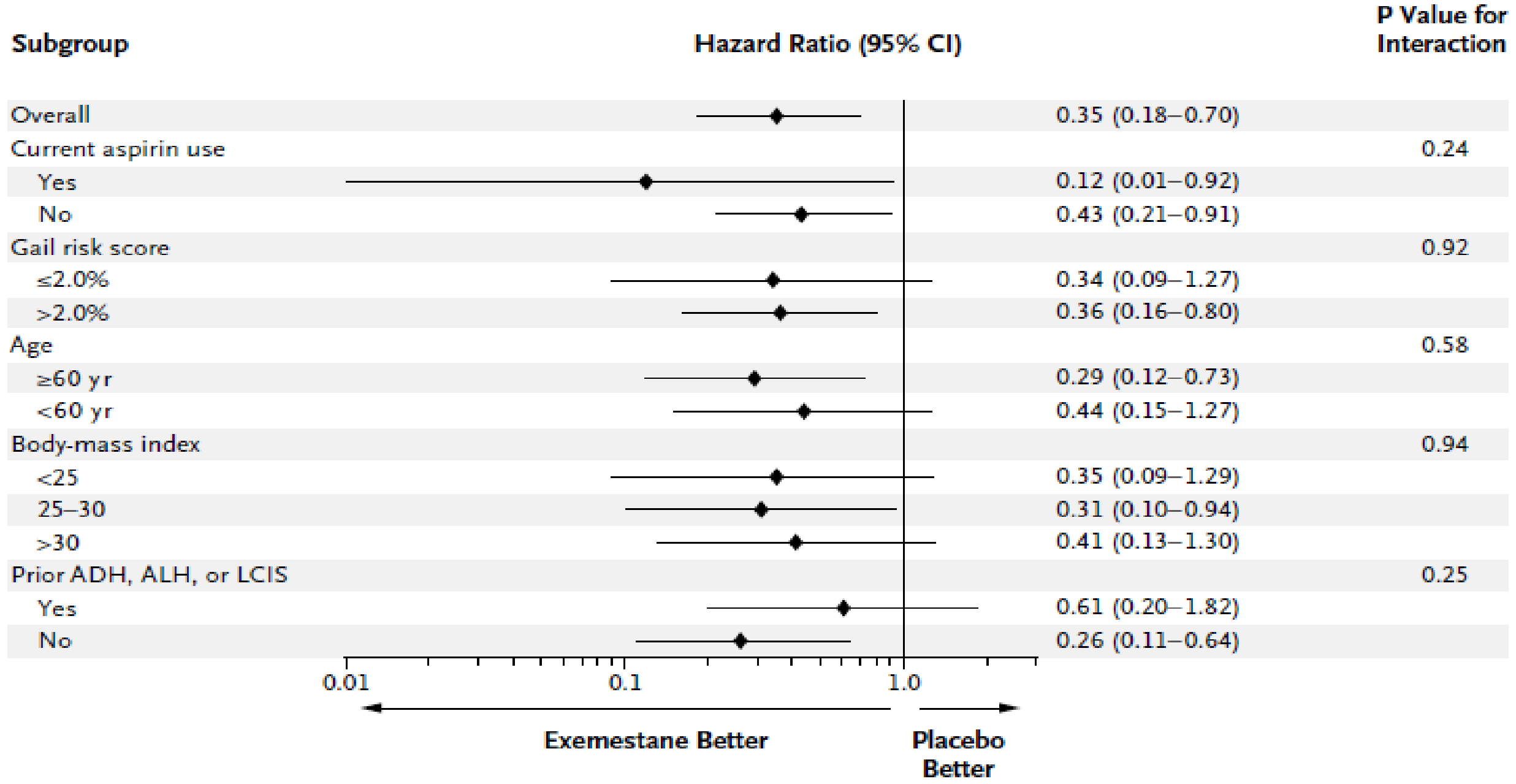


Figure 2. Hazard Ratios for the Development of Invasive Breast Cancer, According to Planned Subgroup Analysis.

MAP.3- Adverse Effects

Adverse Effect	EXEMESTANE (n=2240)	PLACEBO (n=2248)	P value
Any	88%	85%	0.003
Hot flashes	40%	32%	<0.001
Fatigue	23%	21%	0.03
Insomnia	10%	8%	0.04
Diarrhea	5%	3%	0.002
Nausea	7%	5%	0.04
Arthritis	11%	9%	0.01
Clinical skeletal #	6.7%	6.4%	0.72

MAP.3 - QOL

Overall Health-Related QOL (SF36)	Menopause-specific QOL (MENQOL)
• No overall statistically significant difference →Statistically significant worsening in the domain of bodily pain p<0.001	• Physical p=0.12 • Vasomotor p <0.001 • Psychosocial p=0.73 • Sexual p=0.01

MAP.3 – Critique

STRENGTHS	LIMITATIONS
• Sample size calculation attained • Prognostic factors well balanced • Blinded → but not described • Intention-to-treat analysis • Clinical outcomes: meaningful, QOL • Low potential for bias	• Generalizable - white North American women (> 90%) • No explicit description of recruitment • ?? Celecoxib • Definition of “high risk” • Short median f/u 3 yrs • 4% completed 5 years of treatment

MAP.3 – Study Conclusions

- "Significantly ↓invasive breast CA in postmenopausal women who were at moderately increased risk"
- "NNT=94 to prevent 1 case of invasive breast CA with 3 yrs of exemestane"
  - Projected NNT=26 with 5 years
- "….no serious toxic effects and only minimal changes in health-related QOL"

MAP.3 – My Conclusions & Thoughts

- NNT= 108 ♀ to prevent 1 case of invasive breast CA with **3 yrs** of exemestane
- 4% ♀ completed 5 yrs of exemestane
- ↑ arthralgia & menopausal sx (hot flashes, insomnia)
- ? optimal duration unknown
- ? treatment if develop breast CA
- benefits & risks

Case - AJ

- No phase III chemoprevention trial data in BRCA1 or BRCA2 mutations carriers
- GAIL 5 year risk = 1.3%
  - BRCA1 gene mutation significantly ↑ risk
  - IBIS lifetime score = 74 %
- Options:
  - Surveillance
  - Prophylactic surgery (oophorectomy, mastectomy)
  - Chemoprevention?
    - LIBER trial: Prevention of Breast Cancer by Letrozole in Postmenopausal Women Carrying a *BRCA1/2* Mutation

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