

Supervised and Unsupervised Strategies to Identify Medications that Affect Cancer Recurrence Risk

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ROLLINS
SCHOOL OF
PUBLIC
HEALTH

Scope of the public health problem

~14 million new cancer cases per year

Lung, female breast, colorectal and stomach cancers account for more than 40%

Breast cancer ~25% of incident cases in women (~1.7 million cases per year)

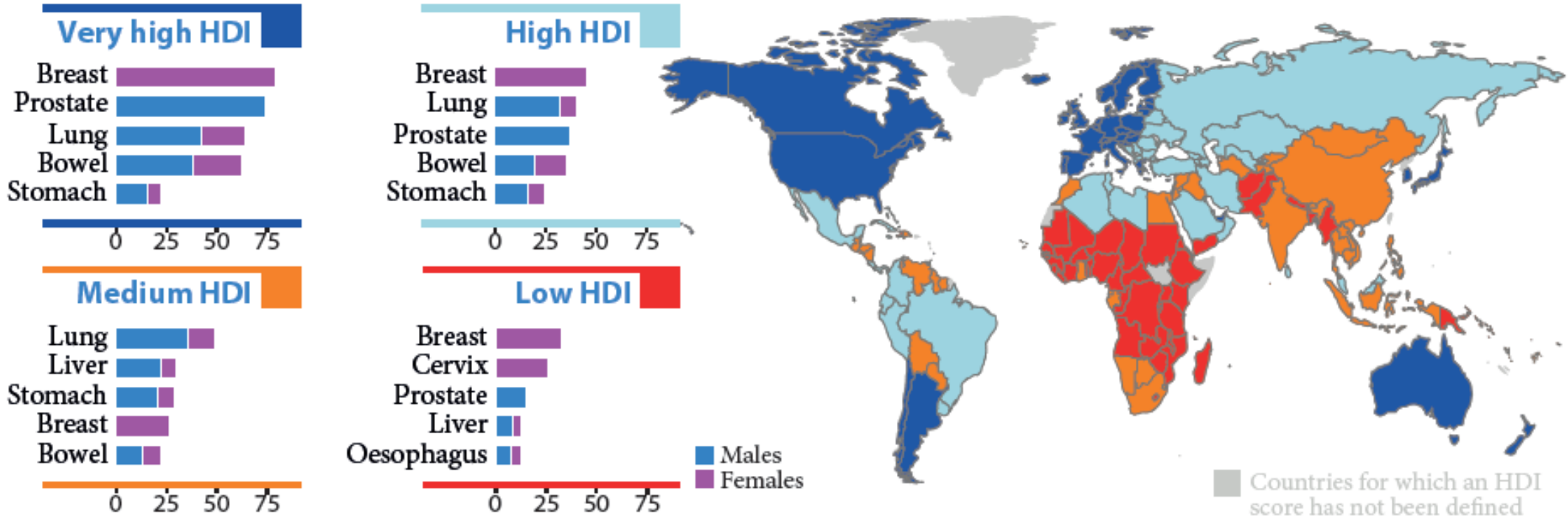
Colorectal cancer 3rd most common incident cancer (~1.4 million cases per year)

As low human development index (HDI) countries develop, their patterns of cancer incidence follow that of high HDI countries

Breast cancer and HDI; incidence

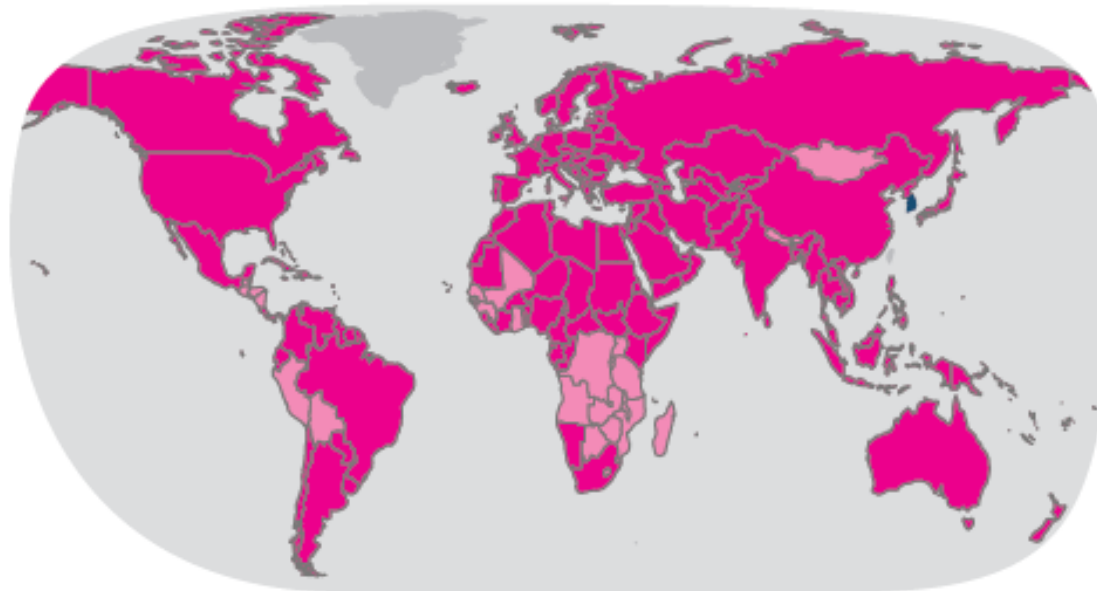
Most commonly diagnosed cancers by Human Development Index

New cases per 100,000 population, age standardised



Females and HDI; prevalence

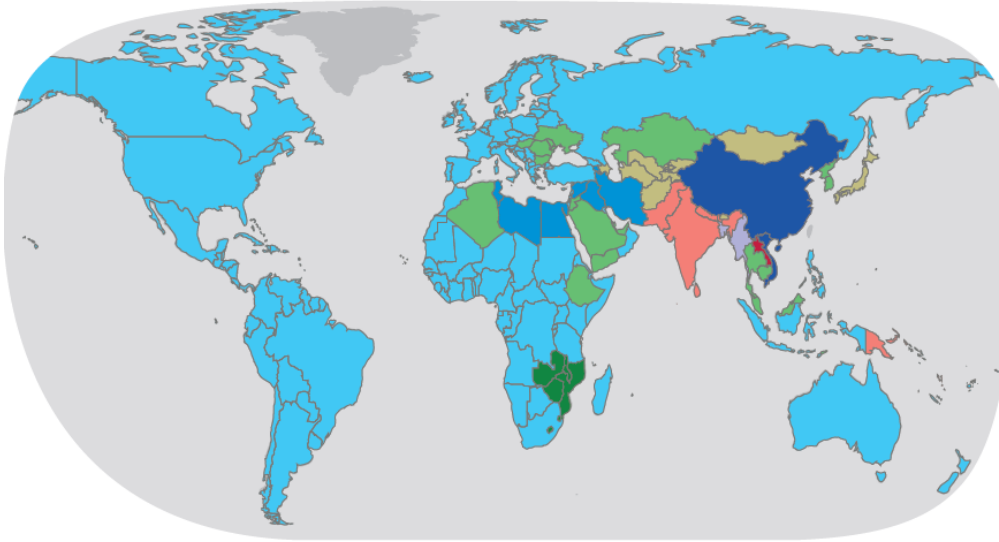
Females



- 1 **Breast** - 151 countries worldwide
- 2 **Cervix** - 30 countries in Africa, the Americas and Asia
- 3 **Thyroid** - South Korea

Males and HDI; prevalence

Males



- 1 Prostate** - 124 countries worldwide
- 2 Bowel** - 23 countries in Africa, Asia and Eastern Europe
- 3 Stomach** - 9 countries in Asia
- 4 Lip, Oral Cavity** - 7 countries in South-Central Asia and Melanesia
- 5 Bladder** - 7 countries in Northern Africa, Asia
- 6 Kaposi Sarcoma** - Lesotho, Malawi, Mozambique, Swaziland, Zimbabwe, Zambia
- 7 Liver** - Gambia, Laos
- 8 Lung** - China, Vietnam
- 9 Pharynx** - Bangladesh, Myanmar

Cancer treatment in low/medium HDI

Low HDI settings

Cancer treatment facilities are not universally available

Life extending treatment is often unavailable, generally for economic reasons

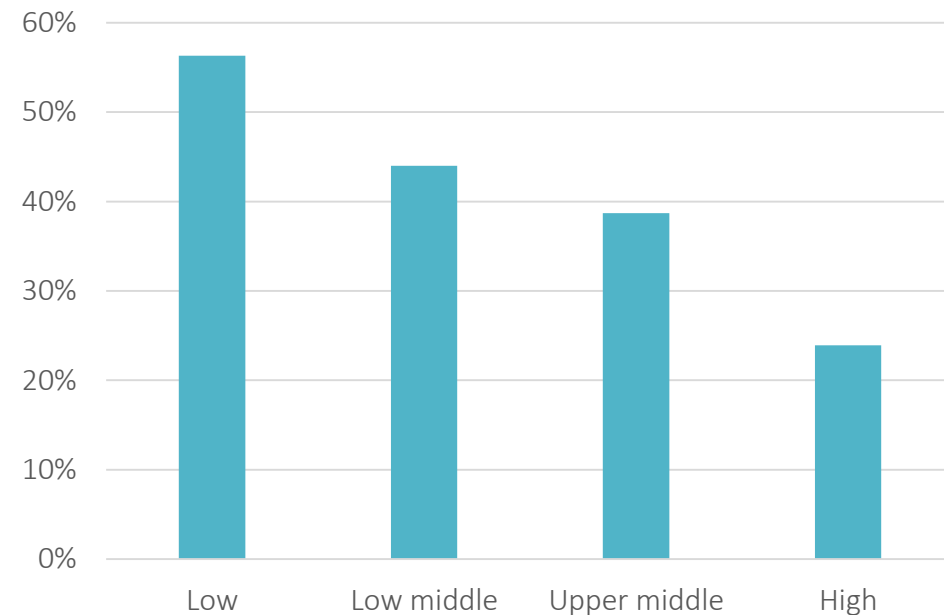
Medium HDI settings

Diagnostic and treatment structures in place

Economic pressures to pay for drugs

Poor training in specialized oncology care

Breast Cancer Fatality
By National Income



Repurposing drugs as potential adjuvant cancer therapy

Many drugs have pleiotropic effects

By and large, these drugs have not been associated with cancer incidence

Emerging evidence suggests some may have antineoplastic effects that may provide adjuvant cancer therapy

Two epidemiologic approaches to identifying candidate drugs

- Supervised: prespecify drugs with potential adjuvant cancer benefit

- Unsupervised: using large databases to agnostically estimate associations

Cardiovascular drugs as potential adjuvant cancer therapy

Many cardiovascular drugs have pleiotropic effects

By and large, these drugs have not been associated with cancer incidence

Emerging evidence suggests some may have antineoplastic effects that may provide adjuvant cancer therapy

- Aspirin

- Anti-hypertensives

- Statins

Aspirin: background

An analgesic, anti-pyretic, and anti-inflammatory drug

Irreversible inhibitor primarily of cyclooxygenase-1

Prevents the progression of existing cardiovascular disease

Reduces the risk of some cancers, especially colorectal cancer



Aspirin: adjuvant breast cancer therapy

Nurses' Health Study (Holmes et al. J Clin Oncol 28:1467-1472)

4164 breast cancer patients within the Nurses' Health Study, 1976 to 2002

Self-reported use of number of days per week using aspirin

Breast cancer mortality as the outcome

Adjusted hazard ratios, compared with never users:

0.91 (95% CI 0.62, 1.33) for once per week users

0.40 (95% CI 0.24, 0.65) for two to five times per week users

0.57 (95% CI 0.39, 0.82) for six to seven times per week users

Not adjusted for statins use

Aspirin: adjuvant breast cancer therapy

Swedish cohort study (Holmes et al. BMC Cancer 2014, 14:391)

27,426 breast cancer patients within the Swedish National Registries, 2005 to 2009

Aspirin prescriptions according to national registries

Breast cancer mortality as the outcome

Adjusted hazard ratios, compared with never users:

1.05 (95% CI 0.87, 1.28) >75% users, up to six months before end of follow-up

Overall, aspirin use was not associated with a lower risk of death from breast cancer

Not adjusted for statins use

Aspirin: adjuvant breast cancer therapy

ORIGINAL ARTICLE

(Epidemiology 2016;27: 586–593)

Low-dose Aspirin, Nonsteroidal Anti-inflammatory Drugs, Selective COX-2 Inhibitors and Breast Cancer Recurrence

*Deirdre P. Cronin-Fenton,^a Uffe Heide-Jørgensen,^a Thomas P. Ahern,^b Timothy L. Lash,^{a,c}
Peer Christiansen,^{d,e} Bent Ejlersen,^{e,f} and Henrik T. Sørensen^a*

34,188 breast cancer patients with median follow-up 7.1 years

5,325 patients developed recurrent disease.

Use of aspirin was not associated with the rate of recurrence (adjusted for statin use)

(HR = 1.0, 95% CI = 0.90, 1.1)

Prediagnostic use was associated with reduced recurrence rates (adjusted for statin use)

(HR = 0.92, 95% CI = 0.82, 1.0).

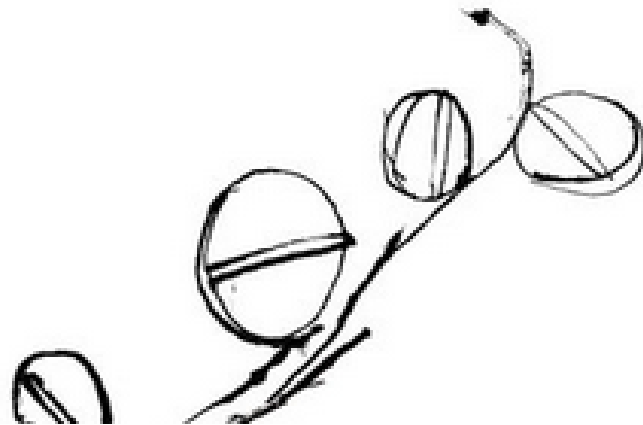
Aspirin: adjuvant breast cancer therapy

The Opinion Pages | OP-ED CONTRIBUTORS

The New York Times

A Cancer Treatment in Your Medicine Cabinet?

By MICHELLE HOLMES and WENDY CHEN MAY 19, 2014



WE believe that it might be possible to treat [breast cancer](#) — the leading cause of female [cancer](#) death — with a drug that can already be found in nearly every medicine cabinet in the world: Aspirin.

Aspirin: adjuvant breast cancer therapy



Let's beat cancer sooner

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Home > Funding for researchers > Research > Who and what we fund > Locations > London > Medical Research Council Clinical Trials Unit > Grants > Trial- A phase III double-blind placebo-controlled randomized trial assessing the addition of aspirin after standard primary therapy in early stage common solid tumours

> **Who and what we fund**

> **Institutions**

> **Locations**

> **London**

> **Medical Research Council Clinical Trials Unit**

> **Ruth Langley**

> **CRUK/12/033: Add-Aspirin Trial- A phase III double-blind placebo-controlled randomized trial assessing the addition of aspirin after standard primary therapy in early stage common solid tumours**

> **Cancer type**

> **Research topic**

Ruth Langley research projects

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CRUK/12/033: Add-Aspirin Trial- A phase III double-blind placebo-controlled randomized trial assessing the addition of aspirin after standard primary therapy in early stage common solid tumours

Funding period: 01 September 2013 to 31 August 2025

Funding scheme: [Phase III Clinical Trial Grants](#)

Funding committee: [Clinical Trials Awards and Advisory Committee](#)

Antihypertensives: background

Class of drugs used to treat hypertension

Adrenergic receptor antagonists (mostly beta blockers)

ACEi (angiotensin converting enzyme inhibitors)

ARBs (angiotensin receptor blockers)

Others (e.g., calcium channel blockers)



Beta blockers: adjuvant breast cancer therapy

Ireland General Medical Services Registry

(Barron et al. J Clin Oncol 29:2635-2644)

Breast cancer patients prescribed propranolol (n=70) or atenolol (n=525) 2001–2006

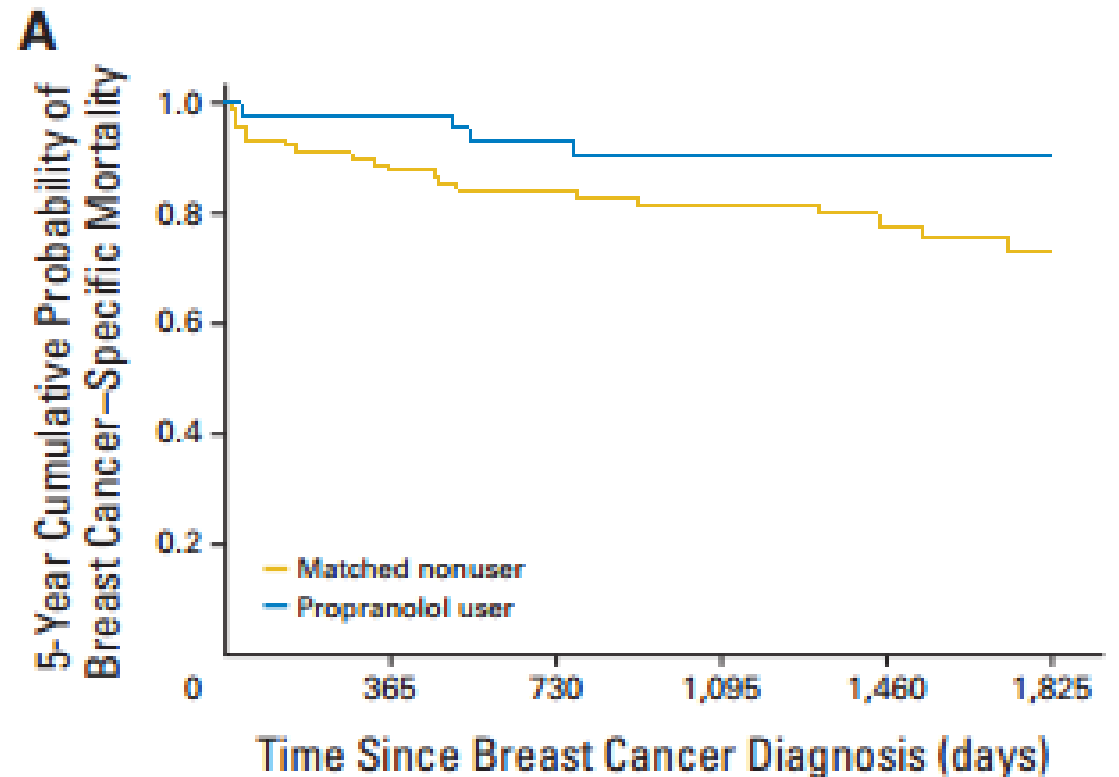
2 to 1 matched non-users of beta blockers

Breast cancer mortality as the outcome

Adjusted hazard ratios, any user compared with never users:

0.19 (95% CI 0.06, 0.60) for propranolol

1.08 (95% CI 0.84, 1.40) for atenolol



Beta blockers: adjuvant breast cancer therapy

MD Anderson Breast Cancer Management System Database (Melhem-Bertrandt. J Clin Oncol 29:2645-2652)

1413 breast cancer patients 1995–2007

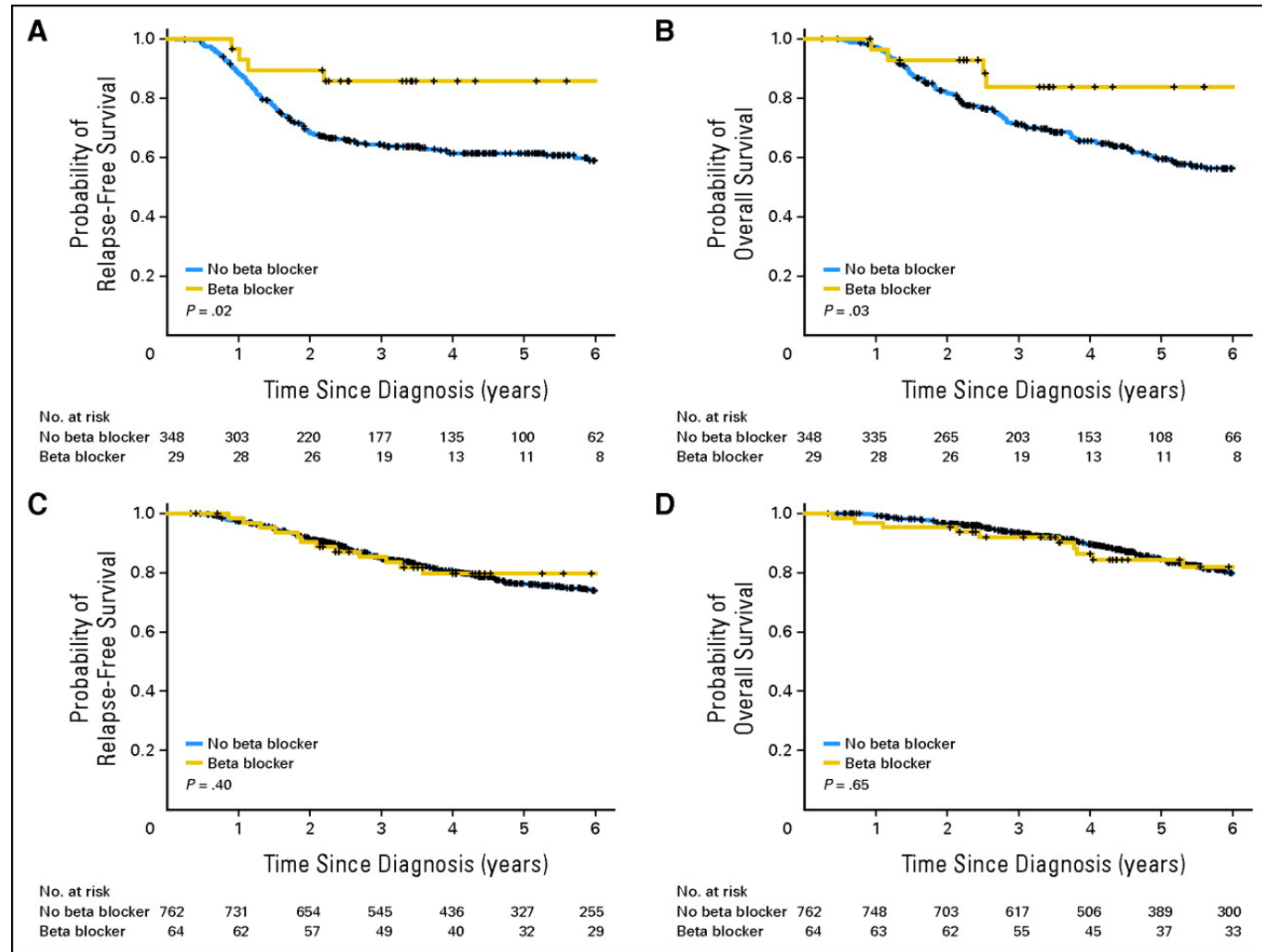
102 beta-blocker users compared with 1311 non-users

Recurrence free survival as the outcome

Adjusted hazard ratios, any user compared with never users:

0.52 (95% CI 0.31, 0.88)

(A) Relapse-free survival (RFS) and (B) overall survival (OS) in patients with triple-negative breast cancer.



Melhem-Bertrandt A et al. JCO 2011;29:2645-2652

Expanding Our Therapeutic Options: Beta Blockers for Breast Cancer?

Patricia A. Ganz, University of California, Los Angeles (UCLA) School of Public Health; Jonsson Comprehensive Cancer Center at UCLA; David Geffen School of Medicine at UCLA, Los Angeles, CA
Steven W. Cole, Jonsson Comprehensive Cancer Center at UCLA; David Geffen School of Medicine at UCLA; Norman Cousins Center for Psychoneuroimmunology at UCLA; and UCLA Molecular Biology Institute, Los Angeles, CA

See accompanying articles on pages 2635 and 2645

In the articles that accompany this editorial, two retrospective studies examine the association between the breast cancer patient's exposure to beta adrenergic antagonist medications and breast cancer recurrence and survival ... The ... articles suggest that these generally safe, inexpensive, and well-understood agents may provide therapeutic leverage in the context of breast cancer as well.

EPIDEMIOLOGY

Beta blockers and angiotensin-converting enzyme inhibitors' purported benefit on breast cancer survival may be explained by aspirin use

**Michelle D. Holmes · Susan E. Hankinson ·
Diane Feskanich · Wendy Y. Chen**

Modeled individually, the multivariable relative risk and 95% confidence intervals (RR, 95 % CI) for breast cancer death were
0.76 (0.54–1.05) for beta blockers
0.89 (0.60–1.32) for ACEIs
0.46 (0.35–0.60) for aspirin.

Modeled simultaneously,
0.83 (0.60–1.16) for beta blockers
1.00 (0.68–1.46) for ACEIs
0.46 (0.35–0.61) for aspirin

Our Danish study

18,733 women diagnosed with an incident invasive breast cancer between 1996 and 2003.

3,414 breast cancer recurrences were recorded with median 6.8 years follow-up

3,660 users of any beta blocker (median 4.7 years of use) 3,075 users of any ACEi (median four years of use) and 1,989 users of any ARB (median 5.0 years of use)

Adjusted hazards ratio (including adjustment for statins)

beta-blockers: 1.3, 95% CI: 1.1, 1.5)

ACEi: 1.1, 95% CI: 0.90, 1.3

ARBs: 0.98, 95% CI: 0.76, 1.3

**I AM CURRENTLY
UNSUPERVISED**
I know, it freaks me out too.
**BUT THE POSSIBILITIES
ARE ENDLESS!**

The unsupervised approach

Have shown the use of Danish cohort of breast cancer patients and use of aspirin or anti-hypertensives.

Linking to all medications and estimating association for each is a marginal additional effort.



ORIGINAL ARTICLE

Concurrent new drug prescriptions and prognosis of early breast cancer: studies using the Danish Breast Cancer Group clinical database

Deirdre Cronin-Fenton^a, Timothy L. Lash^{a,b}, Thomas P. Ahern^c, Per Damkier^{d,e}, Peer Christiansen^{f,g}, Bent Ejlersen^{g,h} and Henrik T. Sørensen^{a,i}

Near null associations

glucocorticoids	ACE inhibitors
aspirin	NSAIDs
selective COX-2 inhibitors	digoxin
opioids	SSRIs

Protective association

use of simvastatin correlates with a decreased risk of breast cancer recurrence

Incident Comorbidities and All-Cause Mortality among Five-Year Survivors of Stage I and II Breast Cancer Diagnosed at Age 65 or Older: A Prospective Matched Cohort Study

Jennifer H. Jordan, PhD¹, Soe Soe Thwin, PhD, MS^{2,3}, Timothy L. Lash, DSc⁴, Diana S.M. Buist, PhD, MPH⁵, Terry S. Field, DSc⁶, Reina Haque, PhD, MPH⁷, Pamala A. Pawloski, PharmD⁸, Hans V. Petersen, MS⁹, Marianne N. Prout, MD, MPH¹⁰, Virginia P. Quinn, PhD⁷, Marianne Ulcickas Yood, DSc, MPH¹⁰, Rebecca A. Silliman, MD, PhD², and Ann M. Geiger, PhD, MPH¹¹

5-year breast cancer survivors insured by one of six US integrated health care systems

Matched with women free of breast cancer

Incident occurrence of new diseases, other than breast cancer, over subsequent 10 years

Results

Older five-year breast cancer survivors did not acquire new diseases more often than matched women free of breast cancer in the subsequent 10 years.

(HR=1.0, 95%CI: 0.93,1.1)

Most common incident comorbidities in the survivor and comparison cohorts were

dementia (18% vs. 19%)

osteoporotic fracture (17% vs. 17%)

congestive heart failure (14% vs. 16%)

cerebrovascular disease (11% vs. 13%)

diabetes (11% vs. 8.6%)

Equivalent individual incident comorbidities during the ten-year follow-up period except for

diabetes (HR=1.4, 95% CI: 1.1,1.8)

MI (HR=0.75, 95% CI: 0.57,0.99)

Cancer history continued to be a hazard for mortality 6–15 years after diagnosis.

(HR=1.3, 95%CI: 1.1,1.4).



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ProBeCaRe

Statins: background

Class of drugs used to treat hypercholesterolemia

Inhibiting hydroxymethylglutaryl-coenzyme A reductase (HMGCoAR)

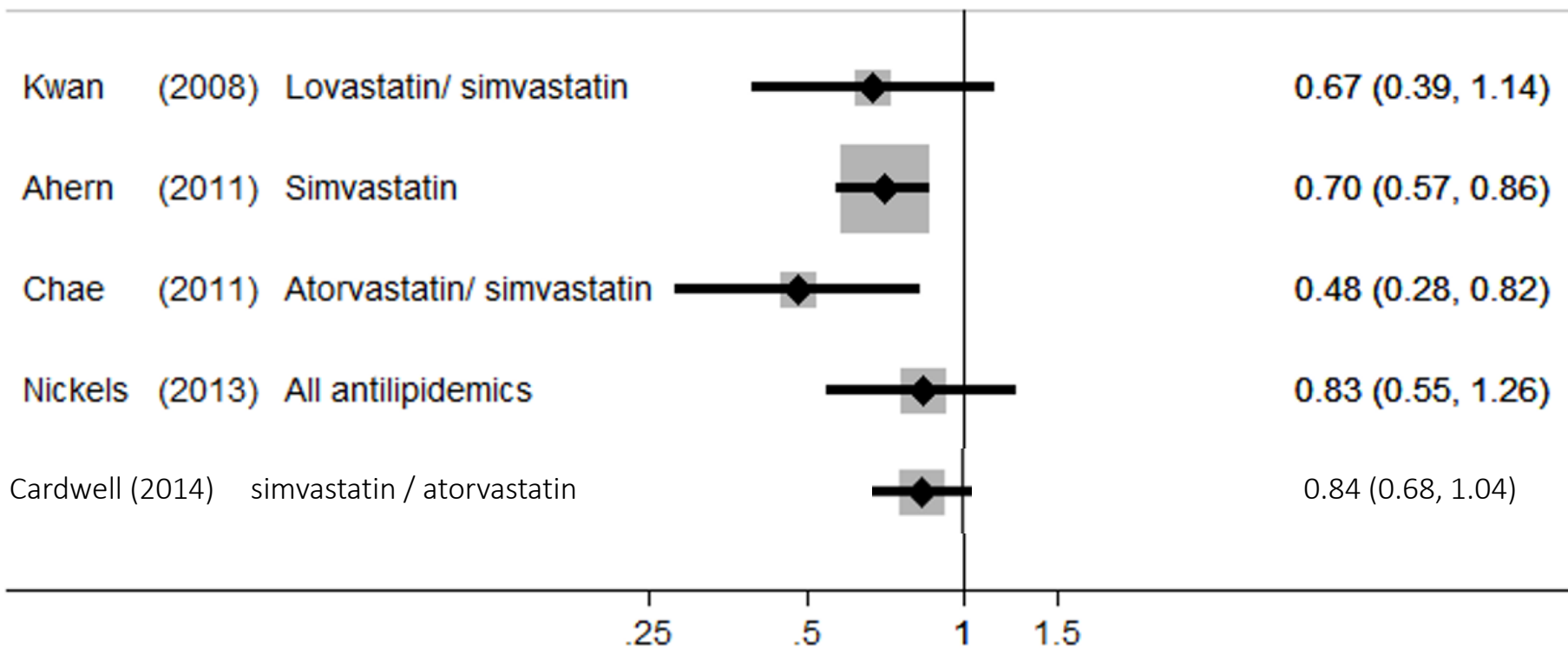
Reduce cardiovascular mortality, acute myocardial infarction, stroke, and arterial revascularization

1994 to 2008 prevalence of statin use among those 30 and older increased from 1.1% to 36% in Northern Denmark



A systematic review and meta-analysis Of 10 studies reported a summary relative risk associating statin use with breast cancer recurrence of 0.64 (95% CI: 0.53 to 0.79).
Int J Cancer. 2016;139(6):1281-1288

Author (Year) Drug exposure(s) RR (95% CI)



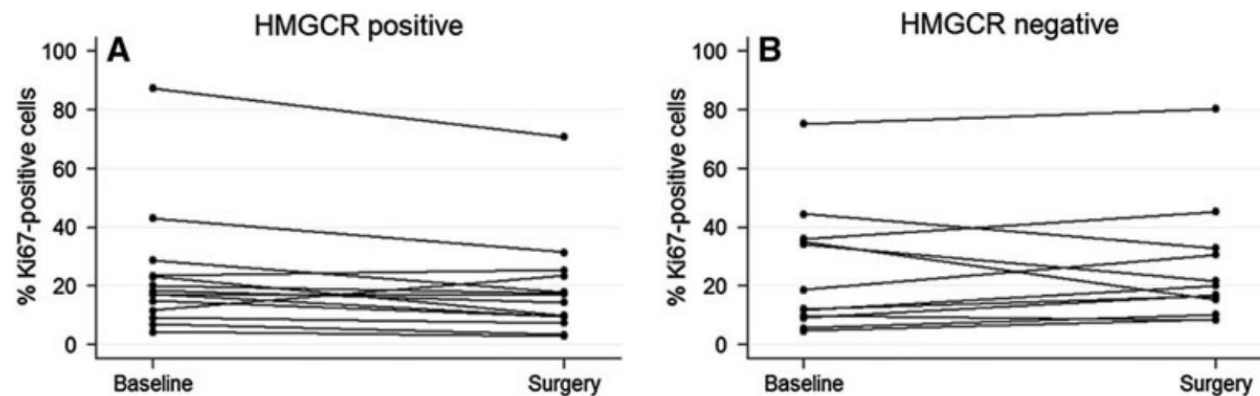
Preliminary evidence: HMG-CoA reductase

Window-of-opportunity trial (2013):

50 patients with invasive breast cancer

Two weeks high-dose atorvastatin (80 mg per day) before surgery.

Paired pre-treatment/post-treatment tumor samples assayed for Ki67 proliferation index & HMG-CoA reductase expression.



24% reduction in Ki67 index in cases whose pre-treatment tumors expressed HMG-CoA reductase

Our study using Danish registries

All female residents of Denmark diagnosed with Stage I-III invasive breast carcinoma, enrolled in the Danish Breast Cancer Cooperative Group (DBCG) registry

Linked cohort roster to the nationwide Danish Register of Medicinal Products to ascertain post-diagnosis prescription drug exposures

Ten years of active recurrence and mortality follow up for all DBCG enrollees (median: 6.8 years).



Our study: statins

18,769 breast cancer patients diagnosed between 1996 and 2003.

18% ever users of statins

92% of statin prescriptions were for simvastatin

3419 breast cancer recurrences

Compared with non-users

aHR=0.80 (95%CI=0.64, 1.0)

$aHR_{\text{simvastatin}}=0.62$ (95%CI=0.46, 0.84)

Five year $aRD_{\text{simvastatin}} = -0.09$ (95%CI= -0.11, -0.08)

Recall that the high HDI to low HDI fatality risk difference is ~22%

Our study: statins

Results were similar when we restricted the analysis to women who did not use statins before diagnosis.

Simvastatin association was similar in strata of ER status, histologic grade, and whether or not a woman received adjuvant radiotherapy.

Competing risks analysis showed the simvastatin association to be similar for specific anatomic sites of recurrence.

Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study

Signe Borgquist, Anita Giobbie-Hurder, Thomas P. Ahern, Judy E. Garber, Marco Colleoni, István Láng, Marc Debled, Bent Ejlersen, Roger von Moos, Ian Smith, Alan S. Coates, Aron Goldhirsch, Manuela Rabaglio, Karen N. Price, Richard D. Gelber, Meredith M. Regan, and Beat Thürlimann

Table 4. Marginal Structural Modeling Results of Initiation of CLM During Endocrine Treatment and Outcome Among All Treatment Arms

Variable	No.	HR	95% CI	<i>P</i>
No. of patients	5,944			
No. of DFS events	1,432			
No. of patients reporting CLM initiation during protocol therapy	697			
DFS model results				
Univariable weighted*		0.81	0.67 to 0.97	.02
Multivariable weighted†		0.79	0.66 to 0.95	.01
No. of BCFI events	940			
No. of patients reporting CLM initiation during protocol therapy	697			
BCFI model results				
Univariable weighted*		0.77	0.61 to 0.97	.03
Multivariable weighted†		0.76	0.60 to 0.97	.02
No. of DRFI events	729			
No. of patients reporting CLM initiation during protocol therapy	697			
DRFI model results				
Univariable weighted*		0.75	0.57 to 0.98	.04
Multivariable weighted†		0.74	0.56 to 0.97	.03

Abbreviations: BCFI, breast-cancer-free interval; CLM, cholesterol-lowering medication; DFS, disease-free survival; DRFI, distant recurrence-free interval; HR, hazard ratio.

*Includes CLM as time-varying covariate.

†Includes CLM and cholesterol as time-varying covariates, with treatment assignment, nodal status, tumor size and grade, peritumoral vascular invasion, and local therapy as covariates in the model. The analysis was stratified by randomization option and prior chemotherapy use.

Table 4. Marginal Structural Modeling Results of Initiation of CLM During Endocrine Treatment and Outcome Among All Treatment Arms

Published in: Signe Borgquist; Anita Giobbie-Hurder; Thomas P. Ahern; Judy E. Garber; Marco Colleoni; István Láng; Marc Debled; Bent Ejlersen; Roger von Moos; Ian Smith; Alan S. Coates; Aron Goldhirsch; Manuela Rabaglio; Karen N. Price; Richard D. Gelber; Meredith M. Regan; Beat Thürlimann; *JCO* 2017, 35, 1179-1188.

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Statins and colorectal cancer outcomes

Summary association with colorectal cancer-specific mortality

Pre-diagnostic statin use: HR=0.80; 95% CI 0.77, 0.84

Post-diagnostic statin use was HR=0.70; 95% CI: 0.60, 0.82 (PLoS One 2015;10(6):e0126944)

Dominated by two large studies, one from Denmark

Pre-diagnostic statin use: HR = 0.81, 95% CI: 0.75, 0.87 (N Engl J Med 2012;367(19):1792-802)

Statins and colorectal cancer outcomes

21,152 Danish early stage colorectal cancer patients, 5036 recurrences, 7084 deaths, and 4066 deaths from colorectal cancer

Use of statins in the preceding year was not associated with the hazard of colorectal cancer recurrence (aHR = 1.01, 95% CI: 0.93, 1.09)

Use of statins in the preceding year was associated with a reduced hazard of death from colorectal cancer (aHR = 0.72, 95% CI: 0.65, 0.79)

Statins and colorectal cancer outcomes

Among the 5036 patients with colorectal cancer recurrence, 20% had used statins in the preceding year.

Use of statins in the year preceding the recurrence was associated with a reduced hazard of colorectal cancer-specific mortality (aHR = 0.83, 95% CI: 0.74, 0.92)

and use of statins in the year preceding the recurrence was associated with a reduced hazard of death from causes except colorectal cancer (aHR = 0.78, 95% CI: 0.61, 1.00)

Statins and the healthy user bias

Thomsen et al (Epidemiology
2013;24:619–620)

Linked Danish health survey to
prescription registry

“We found no evidence of a healthy
lifestyle associated with statin use in
Denmark, which corroborates
observations from England and Wales.

Instead, statin users appeared less
healthy than other persons, with less
healthy personal habits.”

Recurrence outcome is less susceptible to
this bias than breast cancer or overall
mortality

Null for other CV drugs



Mechanisms of antineoplastic action

Inhibition of proliferation by systemic cholesterol reduction

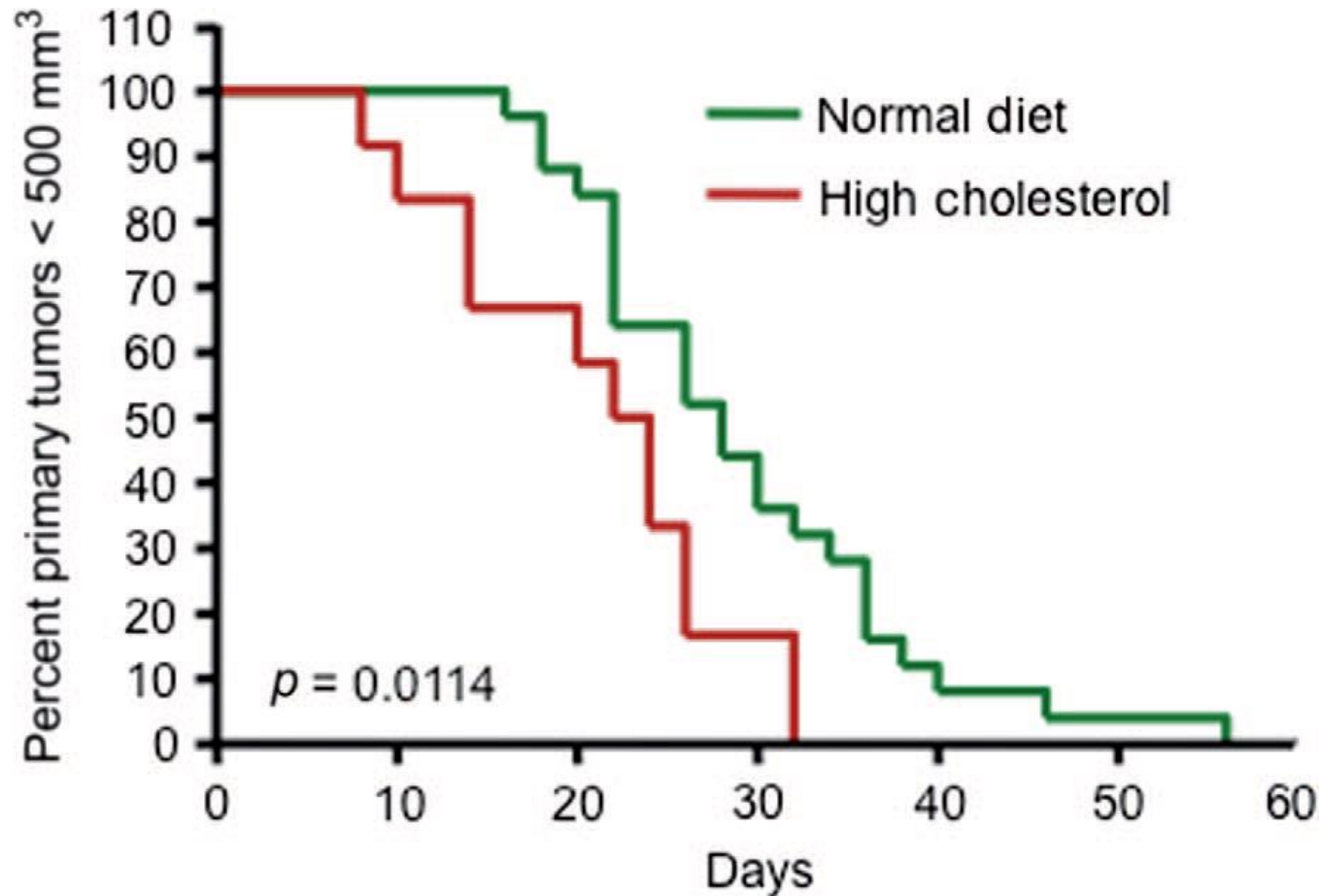
Stimulation of antitumor immune surveillance

Inhibition of tumor-associated HMG-CoAR activity

Interruption of oncogenic signaling by prenylation-dependent proteins

Depletion of 27-hydroxycholesterol—a cholesterol metabolite with a plasma concentration associated with that of total cholesterol—and a breast tumor promoter through estrogen receptor stimulation

Inhibition of proliferation by systemic cholesterol reduction

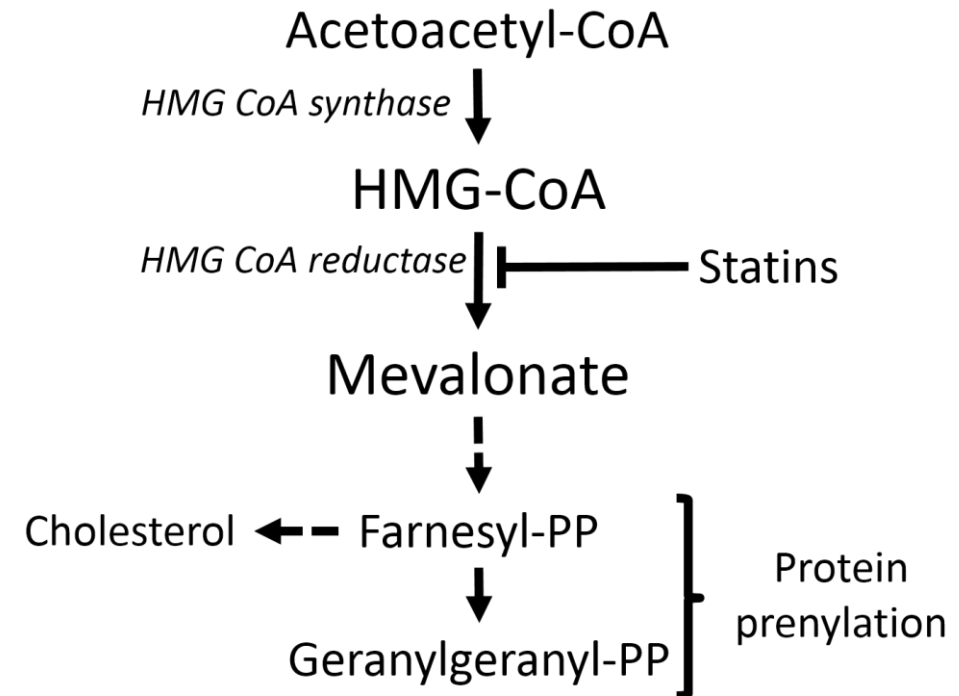


Cholesterol stimulates tumor growth in a mouse model of ER-positive breast cancer. Time zero is onset of palpable tumor after ovariectomy.

Interruption of oncogenic signaling by prenylation-dependent proteins

FPP and GGPP post-translationally prenylate proteins to ensure their correct intracellular localization and function.

Members of the RAS oncogene superfamily depend on prenylation for successful placement in the plasma membrane.



27-hydroxycholesterol & ER α

Circulating levels of 27HC closely mirror those of cholesterol

27HC promotes the proliferation of ER-positive breast cancer cell lines in vitro, but not ER-negative cell lines

27HC functions as an endogenous SERM that exhibits ER-agonist activity

Growth of ER-positive tumors in several different animal models of breast cancer

- Can be stimulated by 27HC administration

- Can be reversed by simultaneous administration of an ER antagonist

Call for a clinical trial

So far, ten observational studies suggest a protective effect of statins on breast cancer recurrence or mortality.

These results are reinforced by experimental studies of statin effects on breast tumor biomarkers.

In Denmark, other cardiovascular drugs are not associated with a reduced risk of recurrence, and statin use is not associated with reduced risk of colorectal recurrence

Additional observational evidence is unlikely to improve the evidence base.

Design considerations for a clinical trial

Choice of drug

- Simvastatin has greatest observational support

- Simvastatin has maximum pleiotropic potential

- Toxicity profile may be a concern (myopathies, including rhabdomyolysis, immunosuppression, insulin resistance)

Management of prevalent and incident hypercholesterolaemia

- Exclude current statins users and those with indications

- Concerns about cross-over: randomize to statins versus usual care

Design considerations for a clinical trial

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Management of prevalent and incident hypercholesterolaemia

- Exclude current statins users and those with indications

- Concerns about cross-over: randomize to statins versus usual care

Longitudinal data on treatment, confounders, and prognostic factors after randomization

- These permit inverse-probability weighting or g-estimation to estimate effects adjusted for exposure crossover, post-randomization confounding, and differential loss-to-follow-up

Collaborators



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The End