A011502 (The ABC Trial) Aspirin for Breast Cancer

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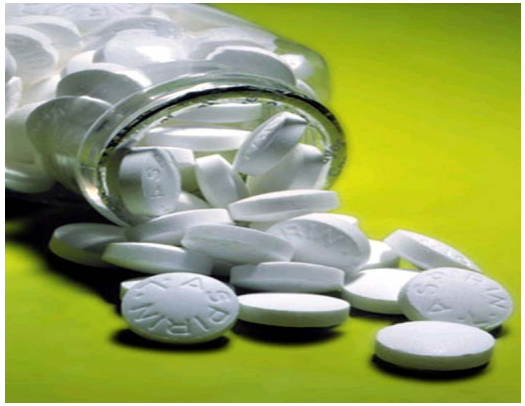
Outline

- Why should aspirin improve breast cancer survival?
  - Epidemiology
  - Clinical trials
  - Mechanisms

- Review of A022502 (Aspirin for Breast Cancer Trial)



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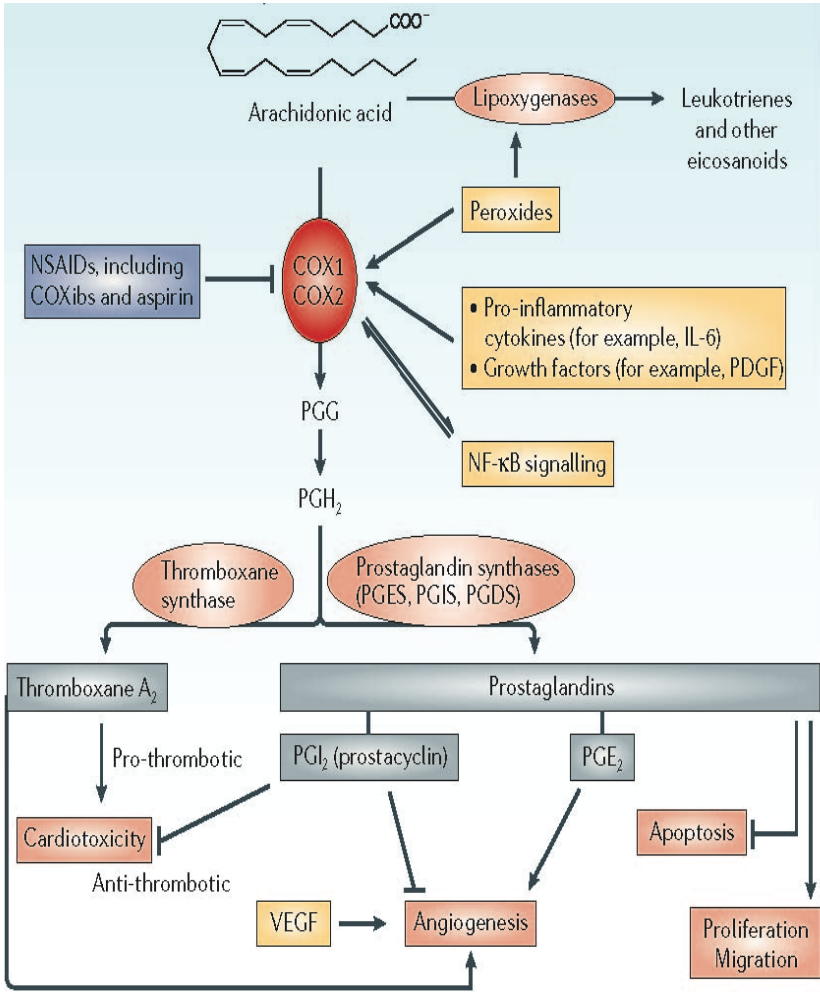
Prostaglandin/COX pathway

- Prostaglandins produced from arachidonic acid via COX pathway (1982 Nobel)
  - Involved in angiogenesis, apoptosis, cell proliferation and migration
- ASA irreversible inhibitor of Cox1 and Cox2
  - ASA $t_{1/2}$ ~20 min
  - Nucleated cells resynthesize Cox
- In vitro and mouse models => ASA/NSAIDs ↓↓ br ca growth and invasiveness



Ulrich, Nat Rev Cancer 2006

EPIDEMIOLOGIC STUDIES OF ASPIRIN AND BREAST CANCER

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Aspirin/NSAIDs and primary prevention

Individual studies inconclusive…

		Cases	RR (95% CI)
Number of tablets per week	<2	826	1.01(0.91-1.13)
	2-5	764	0.95 (0.88-1.15)
	6-14	628	0.92 (0.82-1.03)
	>14	65	0.94 (0.73-1.22)
Number of days per week	<2	936	0.99 (0.89-1.11)
	2-3	529	0.95 (0.84-1.08)
	4-5	547	0.94 (0.83-1.06)
	>5	363	0.91 (0.80-1.05)
Years of use	<=5	351	0.95 (0.83-1.08)
	6-10	365	0.99 (0.87-1.03)
	11-20	602	0.97 (0.86-1.10)
	>20	779	0.92 (0.82-1.03)

Zhang, JCO, 2012

Aspirin/NSAIDs and primary prevention

Type of study	No. of studies	RR (95% CI) fixed effects	RR (95% CI) random effects	Ri	$P_{heterogeneity}$
Aspirin intake only					
All studies	27	0.92 (0.90 to 0.95)	0.87 (0.82 to 0.92)	0.74	<.001
Cohort studies	18	0.95 (0.93 to 0.98)	0.92 (0.86 to 0.97)	0.70	<.001
Case–control studies	9	0.80 (0.75 to 0.85)	0.79 (0.72 to 0.86)	0.39	.12
High intake, all studies	16	0.89 (0.85 to 0.93)	0.86 (0.79 to 0.93)	0.61	.001
High intake, cohort studies	12	0.91 (0.86 to 0.95)	0.88 (0.81 to 0.97)	0.62	.005
High intake, case–control studies	4	0.81 (0.73 to 0.91)	0.72 (0.55 to 0.94)	0.75	.07
Ibuprofen intake only					
All studies	8	0.96 (0.89 to 1.03)	0.79 (0.64 to 0.97)	0.85	<.001
Cohort studies	4	1.00 (0.92 to 1.08)	0.86 (0.66 to 1.12)	0.90	<.001
Case–control studies	4	0.78 (0.64 to 0.94)	0.68 (0.48 to 0.98)	0.69	.05
High intake, all studies	7	1.05 (0.91 to 1.20)	0.85 (0.59 to 1.22)	0.83	<.001
High intake, cohort studies	4	1.10 (0.95 to 1.28)	0.97 (0.64 to 1.46)	0.86	<.001
High intake, case–control studies	3	0.78 (0.54 to 1.12)	0.64 (0.27 to 1.52)	0.82	.01

Takkouche, JNCI 2008

RCT of ASA for primary prevention

Women's Health Study

- 39,876 women aged 45+ randomized to ASA 100 mg QOD vs placebo for 10 yrs
  - Median f/u: on trial = 10.3 yrs; post-trial =17.5 yrs
- RR 0.98 (0.90-1.07) for breast cancer (n=2070)
- RR 0.88 (0.77-1.00) for metastatic cancer and HR 0.73 (0.56-0.96) for metastatic adenocarcinoma

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Cook, Ann Intern Med 2013

Aspirin and breast cancer survival

NURSES' HEALTH STUDY RESULTS

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Nurses' Health Study (NHS)

- 121,700 female registered nurses aged 30-55 in 1976
- Followed prospectively every 2 years with questionnaires updating disease development, medications, lifestyle factors
- Breast cancers confirmed by medical record review

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Study population

- Women with stages I, II, or III breast cancer
- Diagnosed between 1976 and 2002
- Followed until
  - Death
  - June 2006

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Aspirin Assessment

- First asked on 1980 questionnaire
- Baseline for current analysis: 1st questionnaire after diagnosis
  - Excluded 1st year after dx to avoid active treatment period
  - Updated every 2 years
- Categories of use
  - Days per week
  - Tablets per week

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NSAID and Acetaminophen use

- First assessed in 1990
  - Less follow-up time/power than aspirin analysis
  - Similar categories of use to aspirin
  - NSAID mostly ibuprofen

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Endpoints

- Death from breast cancer
- Death from any cause
  - Physician review of death certificates to ascertain cause of death
- Distant recurrence
  - Based upon self-report
    - 92% sensitivity & specificity
  - If not available and patient died of breast cancer, set at 2 ½ years prior to death

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Statistical analyses

- Cox proportional hazards models
- Time varying covariates

- Age
- Stage
- Calendar year
- Body mass index & weight gain
- Smoking
- Physical activity
- Protein/energy intake
- Radiation
- Chemotherapy
- Hormonal therapy
- Menopausal status & menopausal HT
- Oral contraceptive use
- Age at 1st birth/parity

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RESULTS

4,164 participants with Stages I-III cancer

Mean follow-up 10.8 yrs

=>341 breast cancer deaths

=>400 distant recurrences

=>732 deaths from any cause

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Demographics by baseline aspirin use

	Aspirin Use (days/week)				
	Never	Past	Current 1 day/wk	Current 2-5 days/wk	Current 6-7 days/wk
Mean BMI (kg/m^2) at dx	**25**	**26**	**25**	**25**	**26**
Physical activity (MET hrs/wk)	**15**	**16**	**17**	**16**	**16**
Current Smoker at dx (%)	**16**	**14**	**20**	**19**	**17**
Stage I (%)	**58**	**59**	**62**	**61**	**61**
Stage II (%)	**35**	**35**	**33**	**35**	**35**
Stage III (%)	**6**	**7**	**6**	**5**	**4**
ER positive (%)	**81**	**81**	**79**	**76**	**80**
Chemotherapy (%)	**38**	**41**	**34**	**35**	**39**
Hormonal therapy (%)	**68**	**70**	**58**	**64**	**72**

=> No real difference in covariates by aspirin use

Risk of breast cancer death by aspirin use

	Days/Week of Aspirin Intake (Relative risk, 95% confidence interval)					P for Trend
	None	Past	Current, 1	Current, 2-5	Current, 6-7	
Deaths	56	173	44	16	49	
Simple	1.0 (ref)	**0.85** (0.62-1.15)	**1.04** (0.70-1.55)	**0.27** (0.15-0.47)	**0.31** (0.21-0.46)	<0.0001
Multivariate	1.00 (ref)	**0.88** (0.64-1.22)	**1.07** (0.70-1.63)	**0.29** (0.16-0.52)	**0.36** (0.24-0.54)	<0.0001

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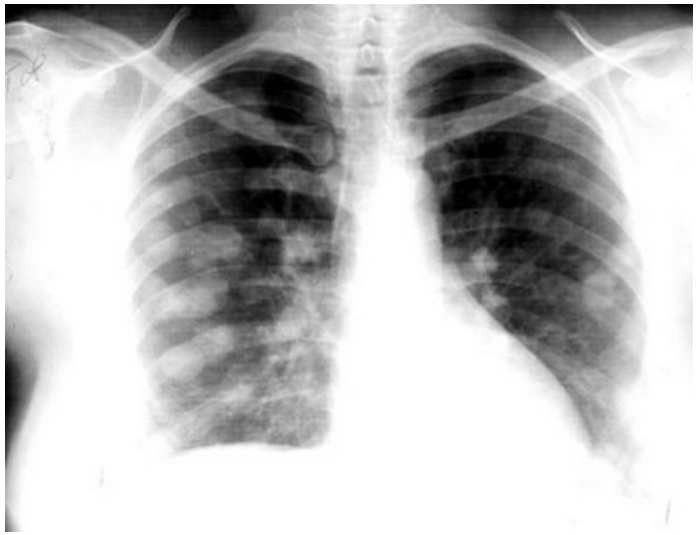
Other Results

- Results for distant recurrence similar



- No effect modification by stage, menopausal status, BMI, ER status

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Other Results

- Effect strongest with *current* use, rather than past or baseline
- Modest duration effect

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Other Results: NSAIDs, Acetaminophen

- 10 fewer years of follow-up since 1st assessed in 1990
  - Limited power
  - Wider confidence intervals

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Risk of breast cancer death by NSAID/acetaminophen

	Days/Week of Use				P for trend
	None/ Past	Current, 1	Current, 2-5	Current, 6-7	
NSAIDs	1.00 (ref)	**1.03** (0.43-2.43)	**1.17** (0.61-2.24)	**0.52** (0.30-0.88)	0.04
Acetaminophen	1.00 (ref)	**2.40** (1.22-4.71)	**1.28** (0.72-2.27)	**1.44** (0.81-2.57)	0.17

- ***Possible survival benefit for NSAIDs***
- ***No association with acetaminophen***
- ***Suggests biological effect of NSAIDS, not confounding***

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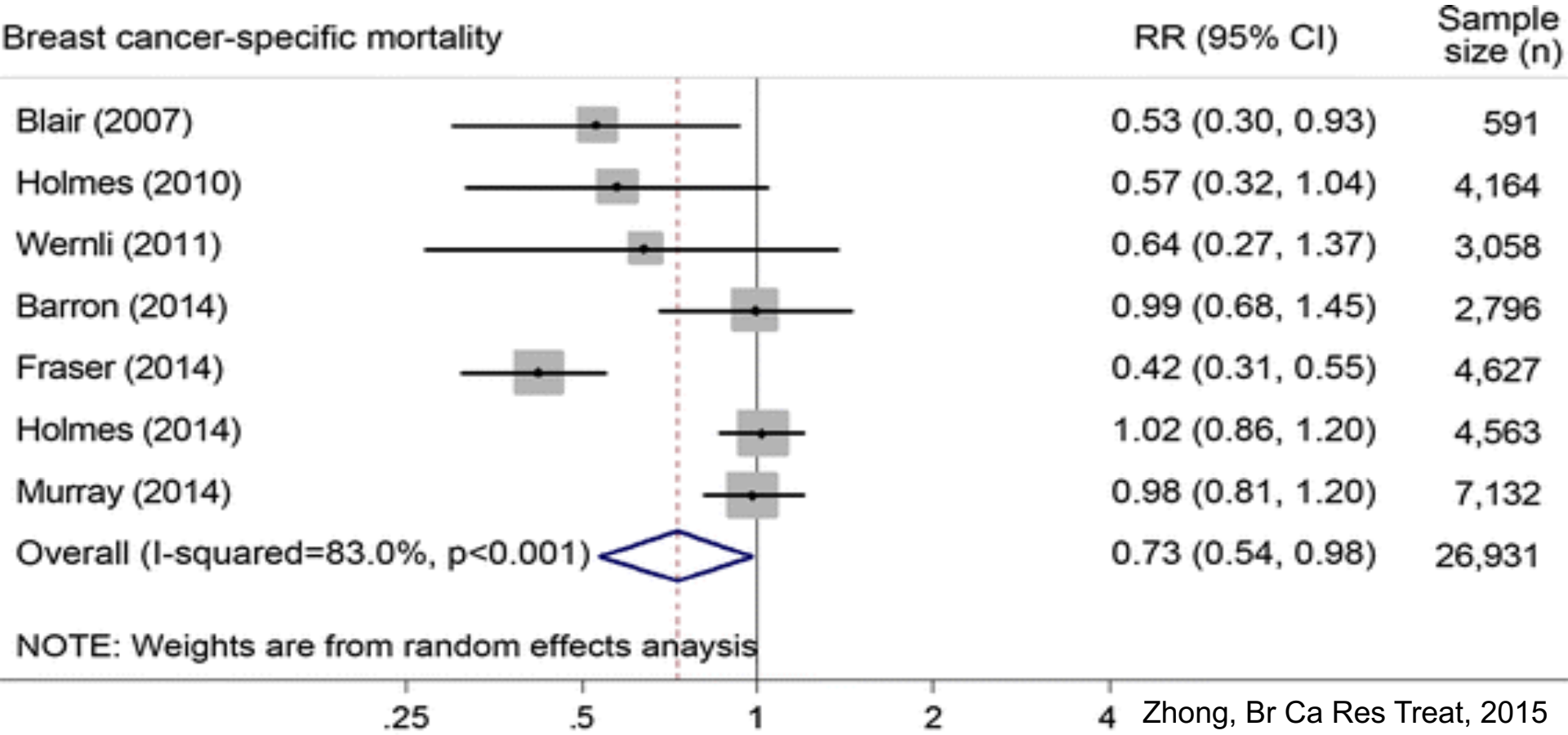
Other studies of ASA and br ca survival

Observational studies: ASA ↓↓ breast ca recurrence

Heterogeneity across studies

European studies use 81 mg ASA, US studies mainly 325 mg



Zhong, Br Ca Res Treat, 2015

CLINICAL TRIAL DATA ON COX2 INHIBITORS FOR BREAST CANCER TREATMENT

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COX2 inhibitors in adjuvant/ neoadjuvant setting

- MA-27: RCT of AI +/- 3 yrs of celocoxib
  - Celecoxib arm closed early after reports of ↑↑ CVD risk

- Neoadjuvant trials
  - Exemestane+celocoxib (n=30)vs exemestane (n=24) vs letrozole (n=28) for 3 month
    - Similar clinical and pathologic response rates
  - Celecoxib (n=22) vs. placebo (n=15) x 2-3 wks pre-op
    - Greater decrease in Ki67 – 29.1 vs 8.2% (p=0.029)
  - Exemestane (n=50) vs celecoxib (n=50) vs placebo (n=25) x 6 wks pre-op
    - No difference in Ki67 with celocoxib

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Goss JCO 2013; Brandao BCR 2013; Chow J Steroid Biochem Mol Bio 2008; Aristarco Cancer Prev Res 2016

RCT of COX-2 inhibitors in metastatic setting

- Phase II study of exemestane +/- celocoxib (n=111)
  - No difference in DFS or TTP, but longer duration of clinical benefit for combination arm (49.1 vs 96.7 wks, no p-value reported)

- Phase III placebo-controlled RCT of exemestane +/- celocoxib (n=157)
  - Terminated early after report of CVD risk with celocoxib
  - No difference PFS, but trend towards benefit in 126 pts treated >3 mths (12.2 vs 9.8 mths, p=0.09)

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Falandry, Br Ca Res Treat, 2009; Dirix, JCO, 2008

RANDOMIZED TRIAL DATA FOR ASPIRIN FROM OTHER DISEASES

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Randomized cardiovascular trial data

Pooled analysis of 5 randomized trials of aspirin (n=17,285)

	Aspirin (cases)	Control (cases)	HR (95% CI)	P-value
All solid cancers with metastases	182	211	0.73 (0.60-0.89)	0.002
Metastatic adenoca	99	135	0.60 (0.46-0.78)	0.0001
Metastatic non-adenoca	83	76	0.96 (0.70-1.32)	0.81
Death due to incident cancer	272	291	0.77 (0.65-0.91)	0.002

=> Most common adenoca – colon, prostate, breast

Rothwell 2012 Lancet

MECHANISMS FOR ASPIRIN

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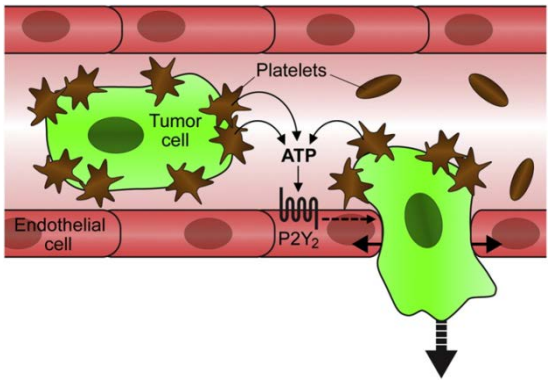
Possible mechanisms for aspirin and breast cancer survival

- Anti-platelet => decrease risk of metastases
  - Supports benefit across several cancers
  - Adjuvant data stronger than primary prevention
  - Discourage adhesion of cancer cells to circulating leukocytes and endothelial cells and disrupt transmigration
  - Protect circulating cancer cells from immune mediated clearance by NK cells
  - Activate TGFB and NFkappaB pathways



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Possible mechanisms for aspirin and breast cancer survival

- Prostaglandin pathway, decrease inflammation
- PI3 kinase/mTOR pathways
  - Colon ca: ASA benefit strongest in PIK3CA mutated
- COX2 pathway
  - COX2 assoc with markers of worse prognosis
  - COX2 and HER2 expression correlated
- Hormonal pathway
  - Prostaglandins may stimulate aromatase and CYP19
  - ASA users have ↓↓circulating estrogen levels

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RANDOMIZED TRIAL OF ASPIRIN AS ADJUVANT THERAPY FOR NODE POSITIVE BREAST CANCER (ABC TRIAL)

Specific aims

1. Randomized placebo-controlled trial of 300 mg aspirin daily among node-positive HER2 negative breast cancer survivors

    a. Primary outcome = invasive disease free survival

2. Assess adherence and toxicity of aspirin

3. Create biospecimen and epidemiologic data repository

    a. Tumor and germline DNA, plasma and urine at baseline and 2 years

    b. Asses lifestyle factors for pro-inflammatory states (e.g. obesity, stress, pain, and sleep)

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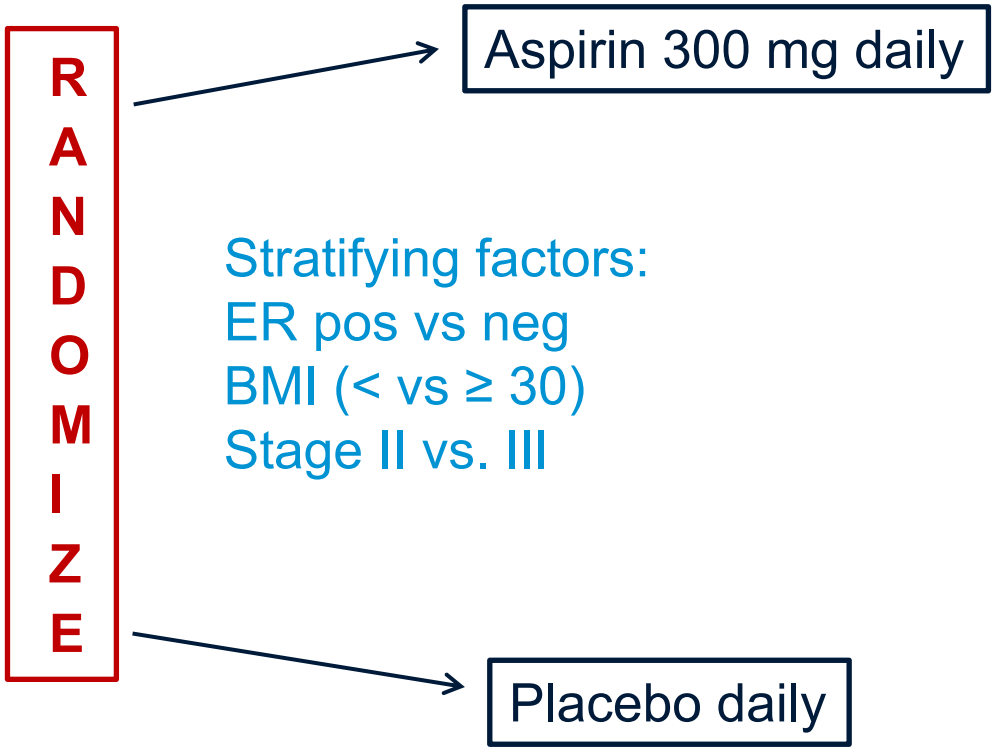
Schema

Node positive (T1-3)

HER2 negative

Within 1 year of dx

Age < 70



Primary endpoint: invasive disease free survival

Accrual goal: 2936 women over 2 years
80% power for HR of 0.75 (assume 5 year iDF survival 77%)

Exclusion criteria

- **Regular aspirin/NSAID users over past year (≥5 days/week)**
  - OK if stop aspirin and/or NSAID's for 1 year prior to study entry and throughout study period
  - Includes stopping baby aspirin
- **History of GI bleeding requiring transfusion or major intervention**
- **History of prior stroke (hemorrhagic or ischemic)**
- **Current anticoagulation with any agent**
- **Uncontrolled hypertension**
- **Prior malignancy within past 5 years**
- **Chronic (duration >30 days) daily use of oral steroids**
- **History of bleeding disorder or chronic thrombocytopenia**
- **History of atrial fibrillation or myocardial infarction**

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Dose modification

- Study treatment terminated for any Grade 3/4 bleeding (requires blood transfusion or major intervention)
- For Grade 2 bleeding, dose reduce to 100 mg
- For Grade 1 bleeding, dose reduction to 100 mg allowed per physician discretion
- Omeprazole 20 mg supplied by study if requested

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Treatment plan and follow-up

- Study drug for 5 years
- Follow up visits every 6 months
  - Recurrence
  - Toxicity
  - Adherence/off protocol aspirin/NSAID use
- Lifestyle measure and tumor optional, but strongly encouraged at baseline and 2 yrs

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Aspirin toxicity

- GI bleeding
  - ↑↑ with age, male gender, and concurrent NSAID use
  - Excess risk of serious GI bleeding in women without risk factors

< age 60	0.4/1000
60-69	1.2/1000
70-79	1.8/1000
>age 79	3.0/1000

  - Meta-analysis of 6 RCT's of ASA vs placebo for CVD: 1.6 vs 0.7% for major bleeding
  - Meta-analysis of 4 polyp prevention studies: 2.79 vs 2.50% for major bleeding
- No difference between plain or enteric-coated
  - PPI can be used for prophylaxis

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Ann Intern Med 2009, Am J Med 2008

Prior Aspirin experience – Women's Health Study

- 100 mg ASA QOD in women for primary prevention
  - ↑ hematuria - 15.2 vs 14.4%
  - ↑ easy bruising - 53.0 vs 42.6%
  - ↑ epistaxis - 19.1 vs 16.7%
  - ↑ GI bleeding requiring transfusion - 0.6 vs 0.5%, p=0.02
  - No difference in stomach upset - 59.5 vs. 59.7%, p=0.59
- Adherence for aspirin vs. placebo
  - Average compliance: 73.7% (placebo) vs 72.5% (ASA),p=0.004
  - Non-trial ASA use (≥ 4 days/month): 13.0% (placebo) vs. 12.7% (ASA), p=0.10
  - Overall compliance ↓↓ with time: 76.1% at 5 yrs and 67.0% at 10 yrs

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NEJM 2005; Diabetes Care 2009

Who should be taking aspirin for CVD/CRC prevention?

- Women aged 50-59 with >10% CVD risk and not increased risk for bleeding
  - Prevent MI, stroke, and colorectal cancer
  - Age strongest risk factor for GI bleeding
- Women aged 60-69 with >10% CVD risk – individualized decision
- No recommendation for women age <50 or >70 for prevention

http://tools.acc.org/ASCVD-risk-estimator/

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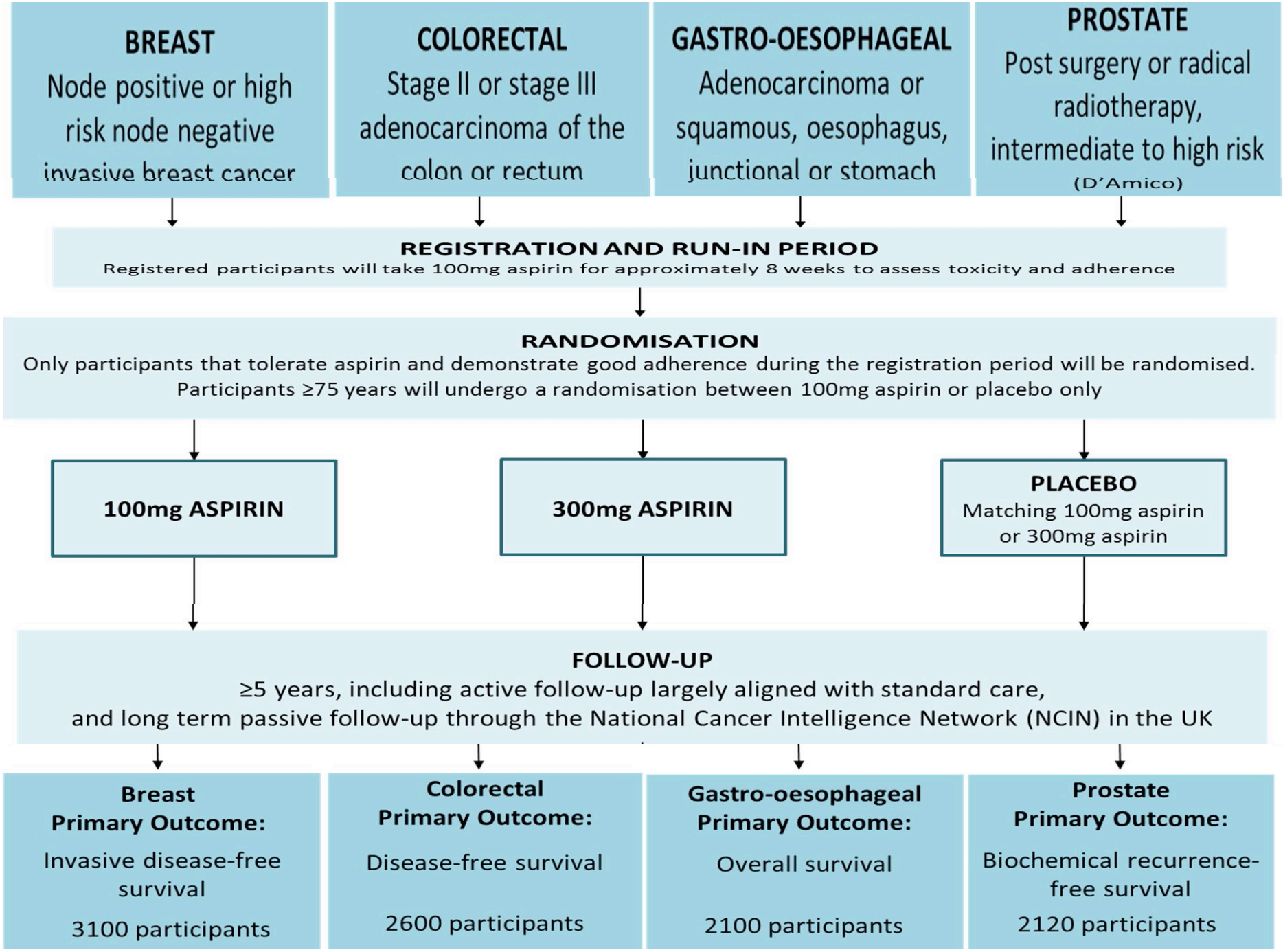
USPTF, Ann Intern Med 2016


BREAST
Node positive or high risk node negative invasive breast cancer
COLORECTAL
Stage II or stage III adenocarcinoma of the colon or rectum
GASTRO-OESOPHAGEAL
Adenocarcinoma or squamous, oesophagus, junctional or stomach
PROSTATE
Post surgery or radical radiotherapy, intermediate to high risk (D'Amico)
REGISTRATION AND RUN-IN PERIOD
Registered participants will take 100mg aspirin for approximately 8 weeks to assess toxicity and adherence
RANDOMISATION
Only participants that tolerate aspirin and demonstrate good adherence during the registration period will be randomised.
Participants ≥75 years will undergo a randomisation between 100mg aspirin or placebo only
100mg ASPIRIN
300mg ASPIRIN
PLACEBO
Matching 100mg aspirin or 300mg aspirin
FOLLOW-UP
≥5 years, including active follow-up largely aligned with standard care,
and long term passive follow-up through the National Cancer Intelligence Network (NCIN) in the UK
Breast
Primary Outcome:
Invasive disease-free survival
3100 participants
Colorectal
Primary Outcome:
Disease-free survival
2600 participants
Gastro-oesophageal
Primary Outcome:
Overall survival
2100 participants
Prostate
Primary Outcome:
Biochemical recurrence-free survival
2120 participants

Conclusions

- Aspirin use after dx associated with 50% ↓↓ risk of breast cancer death
  - Effects seen at frequency > 1 day/week
  - Similar for stages I-III, ER+ vs ER-
  - ↓↓ risk with NSAIDs, but not acetaminophen
- Current use most important
- Not mediated by COX-2
- ABC trial to understand risks and benefits

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Acknowledgements

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- Alliance for Clinical trials in Oncology
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