Research in Pregnancy
Physician Scientist Perspective

George Saade, MD

Professor, OB-GYN and Cell Biology

Chief of Obstetrics and Maternal-Fetal Medicine

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Galveston, TX

utmb Health

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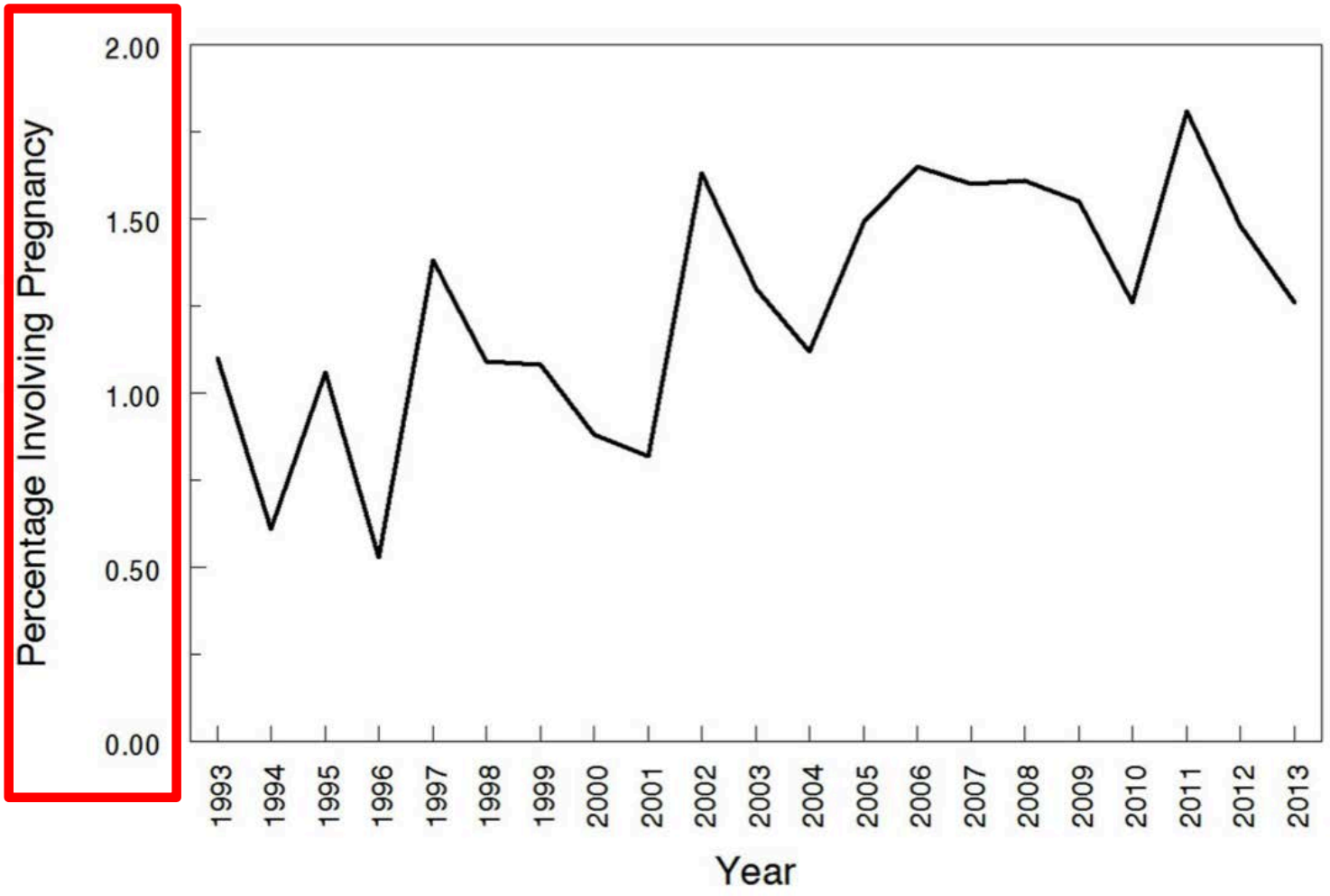
Teratogenicity, while important, is not the only safety concern

Other Concerns in Pregnancy:
Dosing

- Lack of data on dosage
  - Physicians extrapolate drug dosage regimens from non-pregnant subjects
- Can lead to under or overdosing

Proportions of PK trials in pregnancy



McComack & Best. Frontiers 2014

Magnesium Sulfate

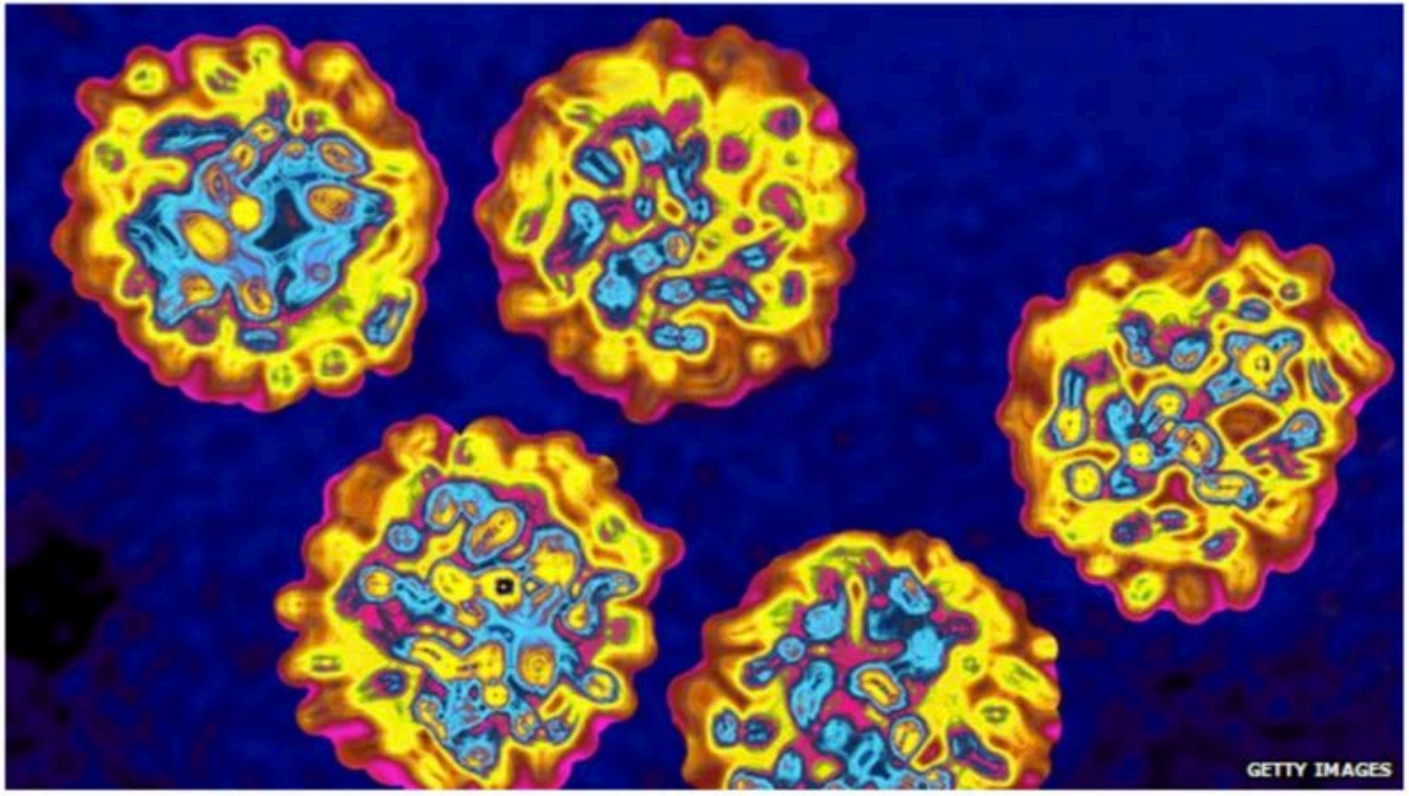
- Many uses in pregnancy
  - Stop premature labor
  - Prevent seizures in women with preeclampsia
  - Protect fetal brain in infants born prematurely

- Dosing regimen
  - No therapeutic level
  - Duration

12 April 2014 Last updated at 01:01 ET

Hepatitis C: New drug treatment 'is a breakthrough'

By Pippa Stephens
Health reporter, BBC News



After 12 weeks, 191 of 208 patients no longer had hepatitis C after being given an oral treatment

A new treatment for hepatitis C "cured" 90% of patients with the infection in 12 weeks, scientists said.

Related Stories

Curing Chronic Hepatitis C — The Arc of a Medical Triumph

Raymond T. Chung, M.D., and Thomas F. Baumert, M.D.

N ENGL J MED 370;17 NEJM.ORG APRIL 24, 2014

It may be possible to imagine the global eradication of HCV infection, but three major challenges remain: infection is often diagnosed at a late stage, the high cost of direct-acting antivirals may lead to selective use, and reinfection remains possible.

What about transmission during pregnancy and childbirth?

Drug studies in pregnancy: Additional examples

- Newer oral anticoagulants
- AED
- SSRI
- MRI and US contrast agents
- Asthma medications

Original Investigation

Acetaminophen Use During Pregnancy, Behavioral Problems, and Hyperkinetic Disorders

Zeyan Liew, MPH; Beate Ritz, MD, PhD; Cristina Rebordosa, MD, PhD; Pei-Chen Lee, PhD; Jørn Olsen, MD, PhD

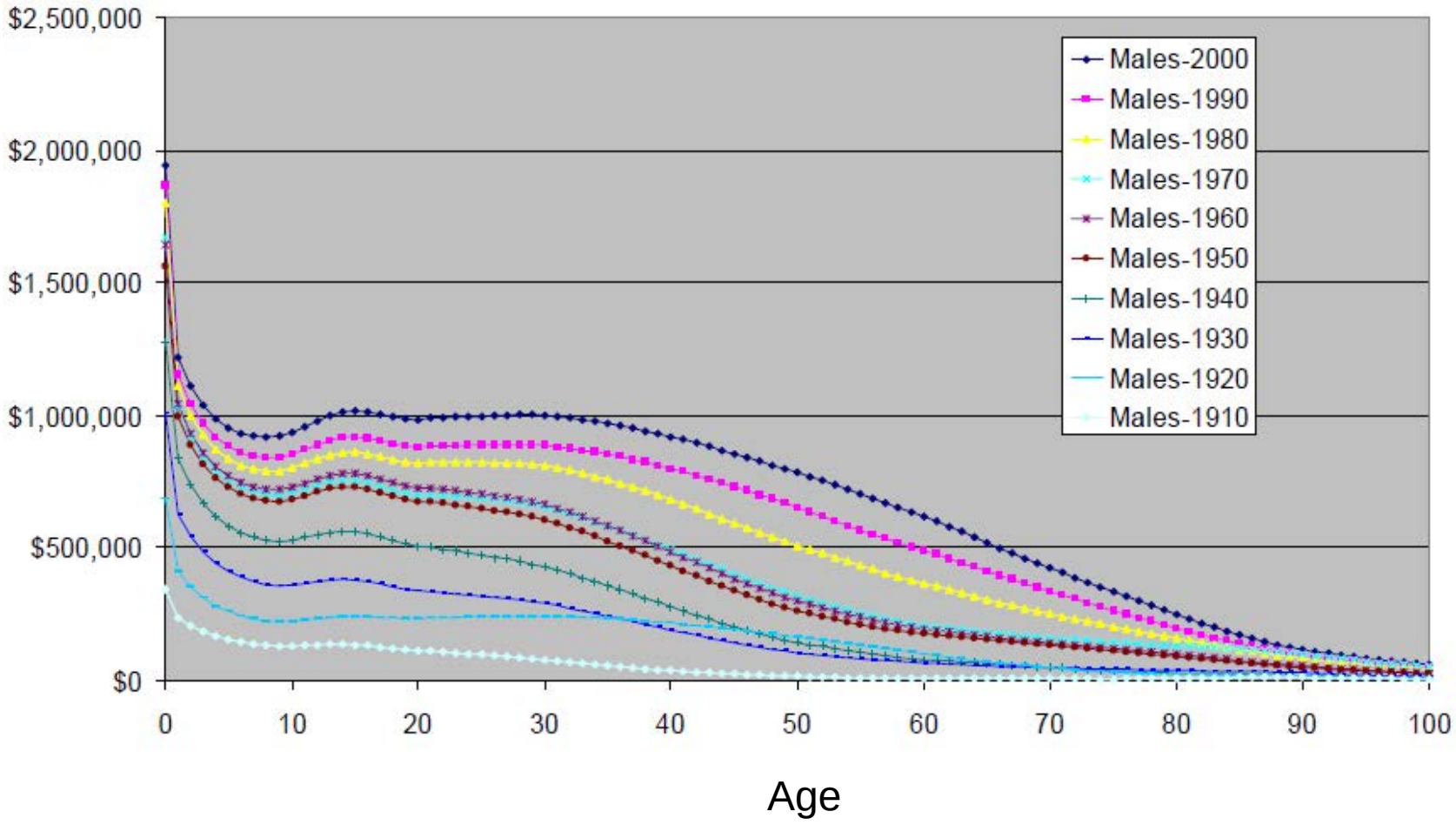
	Hospital-Diagnosed HKD			ADHD Medication		
		Hazard Ratios			Hazard Ratios	
Prenatal Exposure and Timing	No. of Cases (Person-years)	Crude	Adjusted (95% CW	No. of Cases (Person-years)	Crude	Adjusted (95% CW
Acetaminophen use during pregnancy						
Never used	283 (159 209)	1.00	1 [Reference]	478 (170 264)	1.00	1 [Reference]
Ever used	551 (204 042)	1.52	1.37 (l.19-1.59)	877 (217 945)	1.43	1.29 (l.15-1.44)
1st trimester only	88 (34 887)	1.42	1.35 (l.07-1.72)	120 (37 288)	1.15	1.09 (0.89-1.33)
2ndtrimesteronly	43 (18 714)	1.29	1.26 (0.91-1.73)	70 (20 011)	1.25	1.20 (0.91-1.55)
3rdtrimesteronly	103 (41 418)	1.40	1.22 (0.97-1.53)	182 (44 262)	1.47	1.28 (1.08-1.52)
Both1stand2ndtrimesters	37 (14 771)	1.41	1.31 (0.93-1.85)	52 (15 789)	1.17	1.09 (0.81-1.45)
Both2ndand3rdtrimesters	37 (14 009)	1.49	1.30 (0.92-1.84)	77 (14 936)	1.84	1.63 (l.28-2.07)
Both1stand3rdtrimesters	70 (25 291)	1.56	1.41 (l.08-1.84)	116 (26 938)	1.53	1.39 (l.13-1.71)
All3trimesters	120 (36 463)	1.84	1.61 (l.30-2.01)	181 (38 980)	1.65	1.44 (l.21-1.72)

JAMA Pediatrics April 2014 Volume 168, Number 4

What do I see?

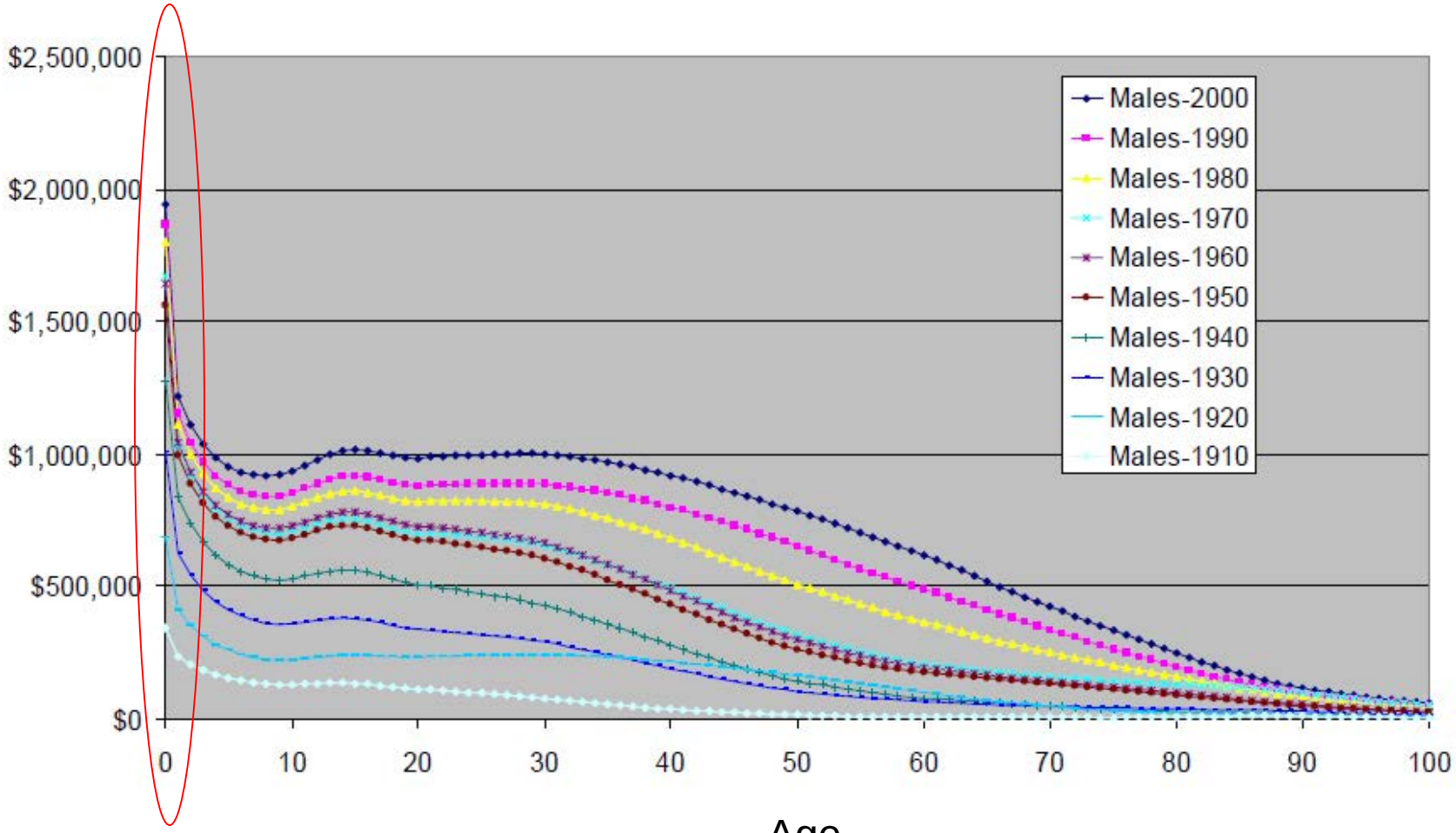
- Very little evidence to guide OB practice
- Clinical research in pregnancy is difficult
  - Involves mother, fetus, family
  - Outcomes are rare
  - Long term follow up
- ROI on clinical research in pregnancy
  - Impacts mother, fetus, family
  - Impacts long term

Cumulative Value of Gains in Longevity by Age in Males



Murphy & Topel 2004

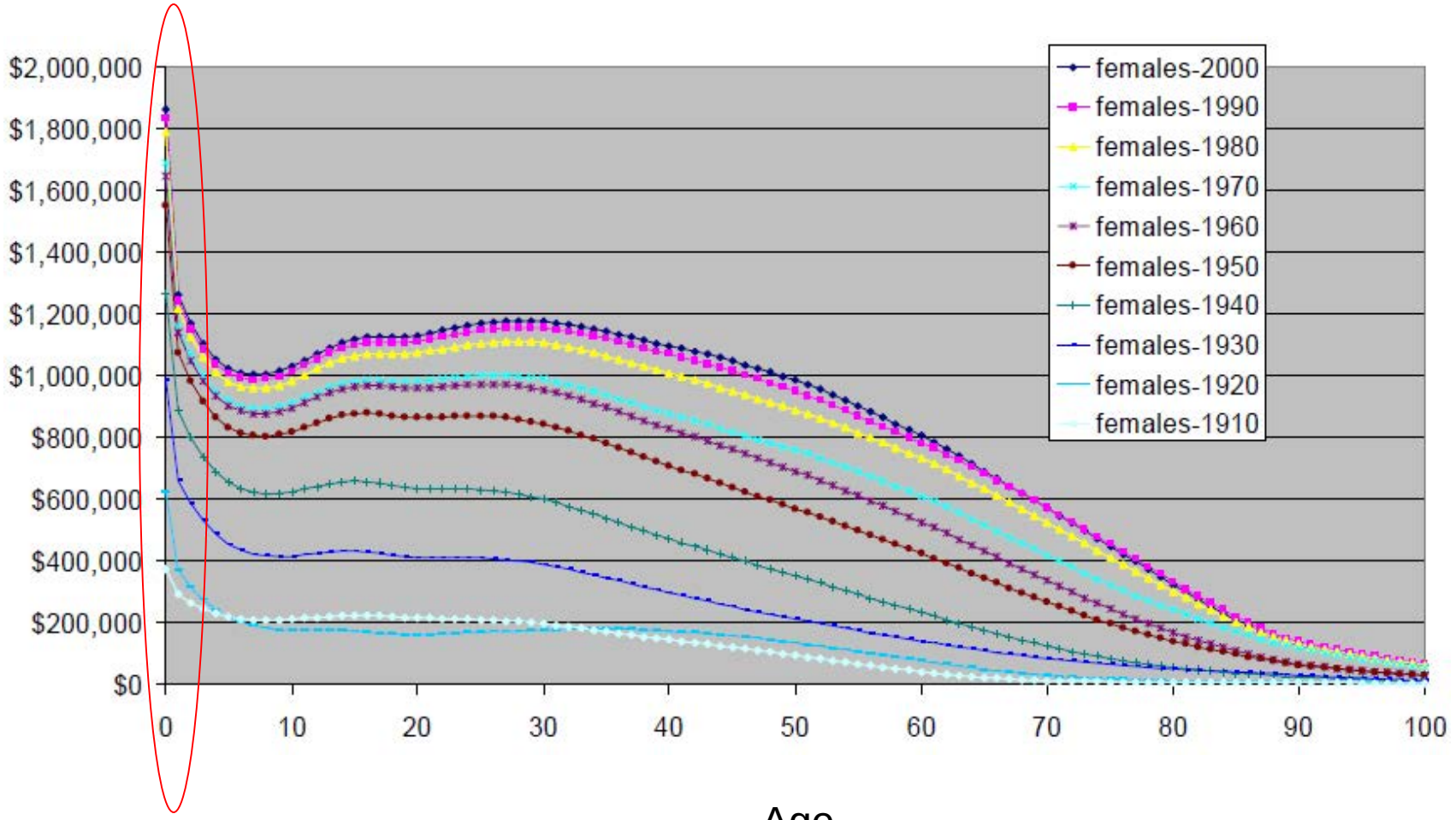
Cumulative Value of Gains in Longevity by Age in Males



Highest at birth

Murphy & Topel 2004

Cumulative Value of Gains in Longevity by Age in Females



Highest at birth

Murphy & Topel 2004

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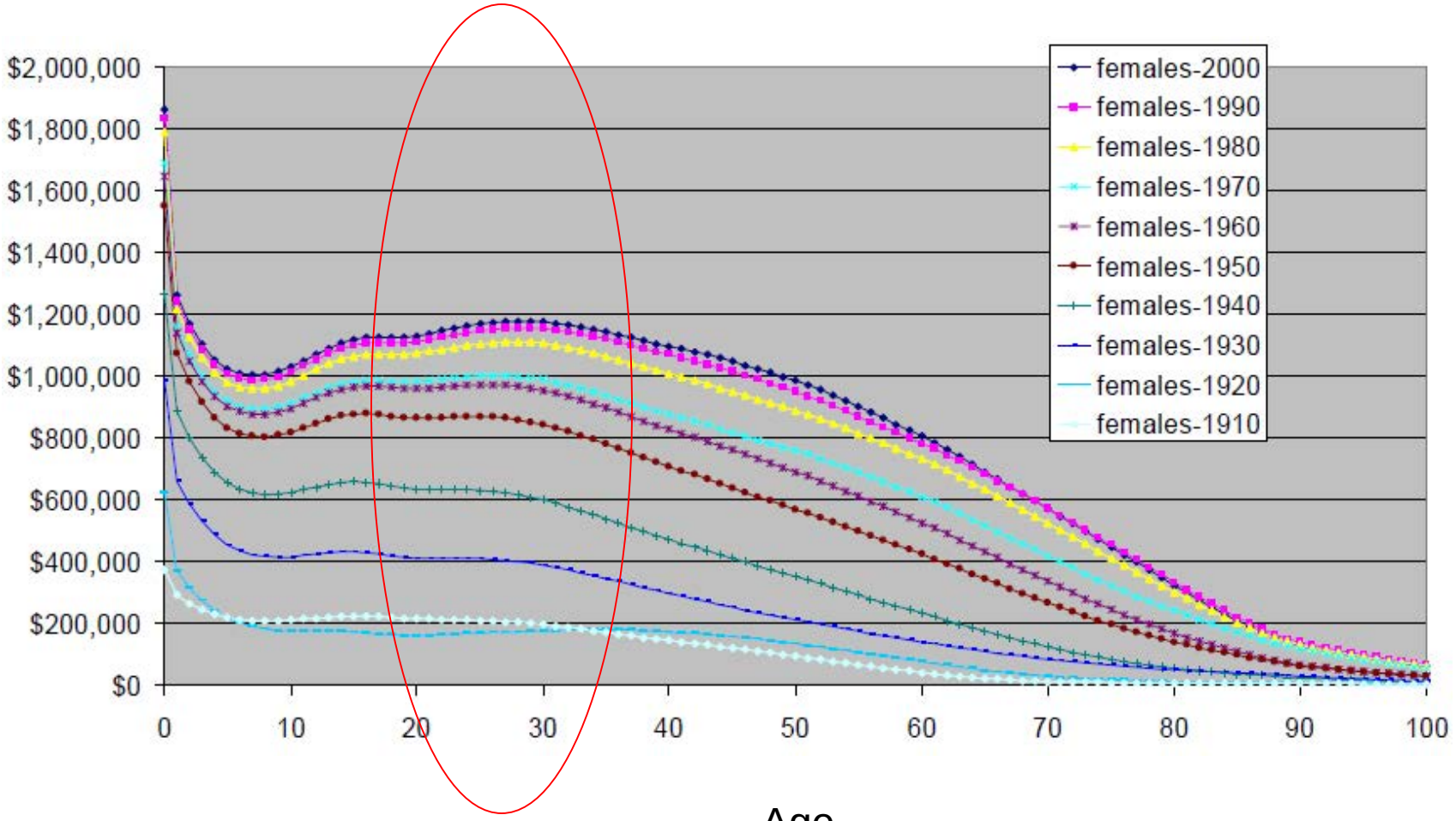

Reproductive age in women is another area

Murphy & Topel 2004

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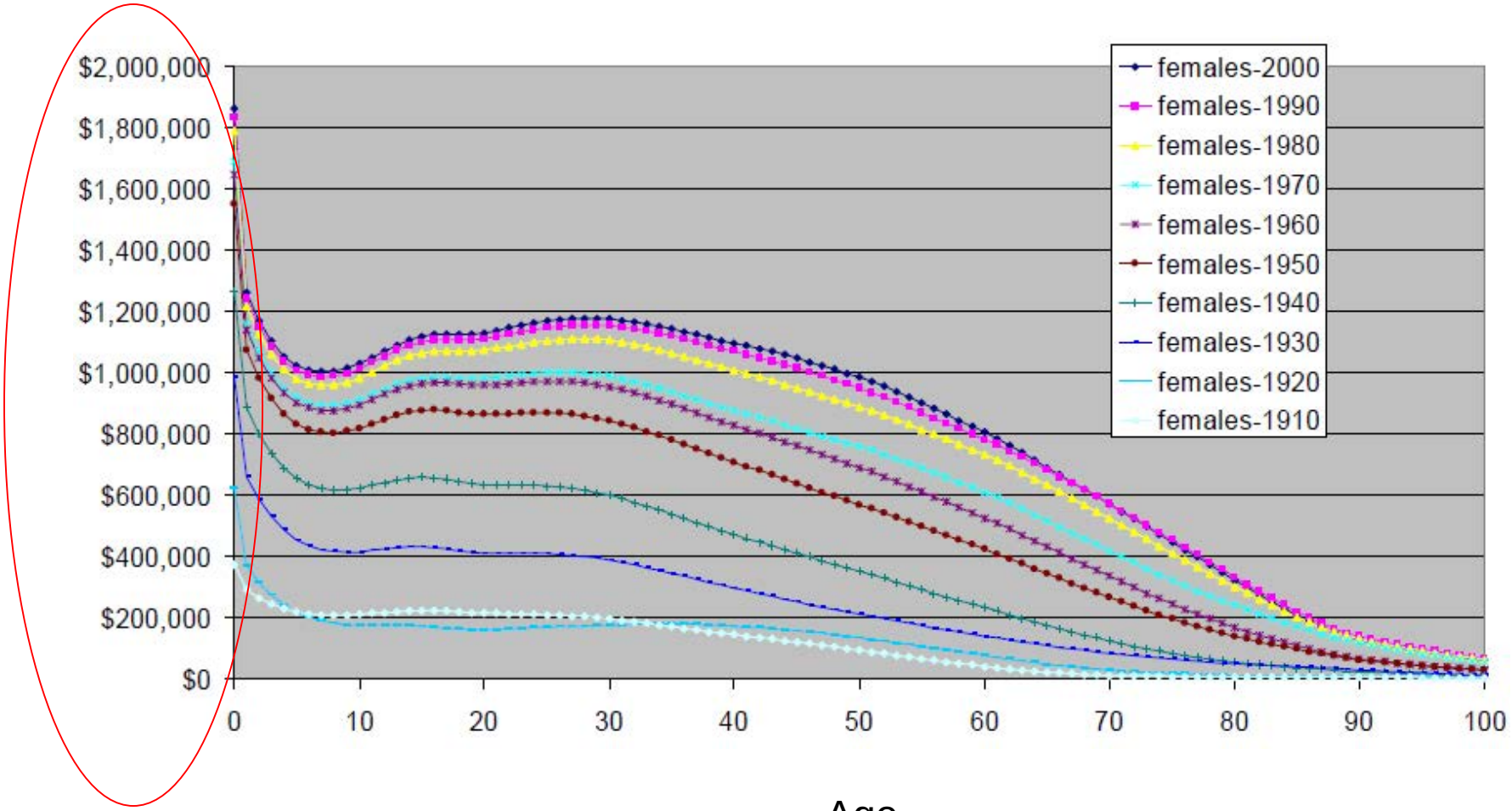

Reproductive age in women is another area

Murphy & Topel 2004

Economic Value of the War on Cancer

Lakdawalla et al. 2010

Cancer	Annual value of survival gains ($)	Lifetime value of survival gains ($)	Implied value of a life year ($)
All combined	30,900	324,149	83,115
Breast	28,066	361,554	100,431
Colorectal	20,588	155,979	91,752
Lung	37,962	68,695	82,765
NHL	33,985	275,055	78,587
Pancreas	44,861	25,817	56,123

In Year 2006 dollars

A War on Obstetrical Complications is Needed

The pregnant women as a drug orphan: a global survey of registered clinical trials of pharmacological interventions in pregnancy

J Scaffidi,[a] BW Mol,[b,c] JA Keelan[d]

BJOG 2017;124:132–140.

Registry	Registry URL	All trials in registry		Trials active January 2013 – December 2014	
		Total *n*	Pregnancy-related drug trials (%)	Total n	Pregnancy-related trials (%)
Clinicaltrials.gov	https://clinicaltrials.gov/	193 645	515(0.27)	128 617	189(0.15)
EU Clinical Trials Register (EU-CTR)	https://www.clinicaltrialsregister.eu/	25 877	188(0 73)	4 543	60 {1.32)
Japan Primary Registry Network (JPRN)	http://rctportal.niph. go.jp/en/	20 157	33(0.16)	11 291	20(0.18)
Australian and New Zealand Clinical Trials Registry (ANZCTR)	www.anzctr.org.au/	15 568	83(0.53)	10 317	40(0.39)
International Standard Registered Clinical/social study Number Registry (ISRCTN)	https://www.isrctn.com/	13 655	227(1.66)	3416	35(1.02)
Iranian Registry of Clinical Trials (IRCT)	http://www.irct.ir/	8333	166(1.99)	3664	63(1.7)
Clinical Trials Registry-India (CTRI)	http://ctri.nic.in/Clinicaltrials/login.php	5905	102(1 73)	N/A	44 (NIA)
Chinese Clinical Trial Registry (ChiCTR)	http://www.chictr.org.cn/enindex.aspx	5198	51 (O 98)	1897	23(1.2)
The Netherlands National Trial Register (NTR)	www.trialregister.nl/trialreg	4980	33(0.66)	N/A	15 (N/A)
German Clinical Trials Register (DRKS)	https://www.drks.de/drks_web/	3634	5 (O 14)	2112	1(0.05)
Health Canada's Clinical Trials Database	http://ctdb-bdec.hc-sc.gc.ca	1485	4(0.27)	1029	4(0.39)
Clinical Research Information Service (CRiS), Republic of Korea	https://cris.nih.go.kr/eris/en	1343	4(0.30)	1138	1(0.09)
Brazilian Clinical Trials Registry (ReBEC)	www.ensaiosclinicos.gov.br/	574	0	306	0 (O)
Pan African Clinical Trial Registry (PACTR)	www.pactr.org/	417	31(7.43)	N/A	26 (N/A)
Thai Clinical Trials Registry (TCTR)	www.clinicaltrials.in.th/	409	8(1 96)	268	6 (2.24)
Cuban Public Registry of Clinical Trials (RPCEC)	http://registroclinico.sld.cu/en/home	193	0 (O)	119	0 (O)
Sri Lanka Clinical Trials Registry (SLCTR)	www.slctr.lk/	165	11(6.67)	109	7 (6.42)

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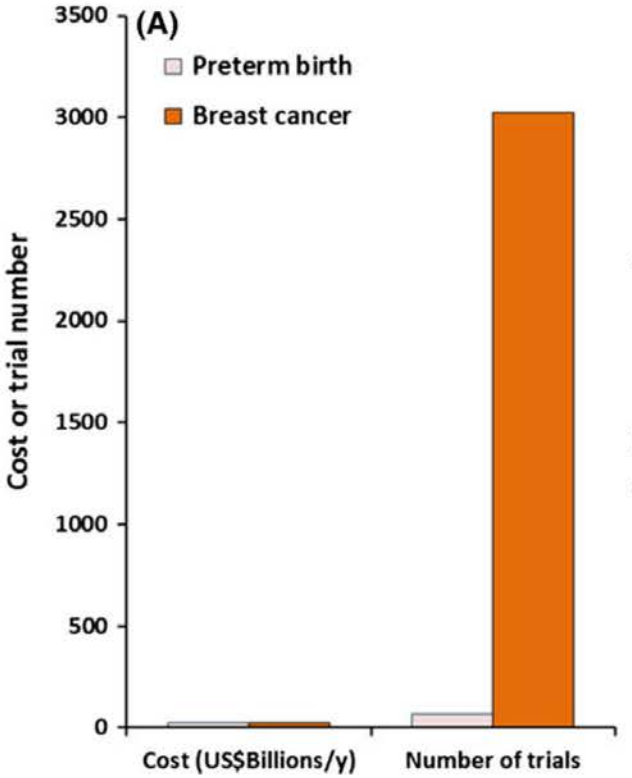

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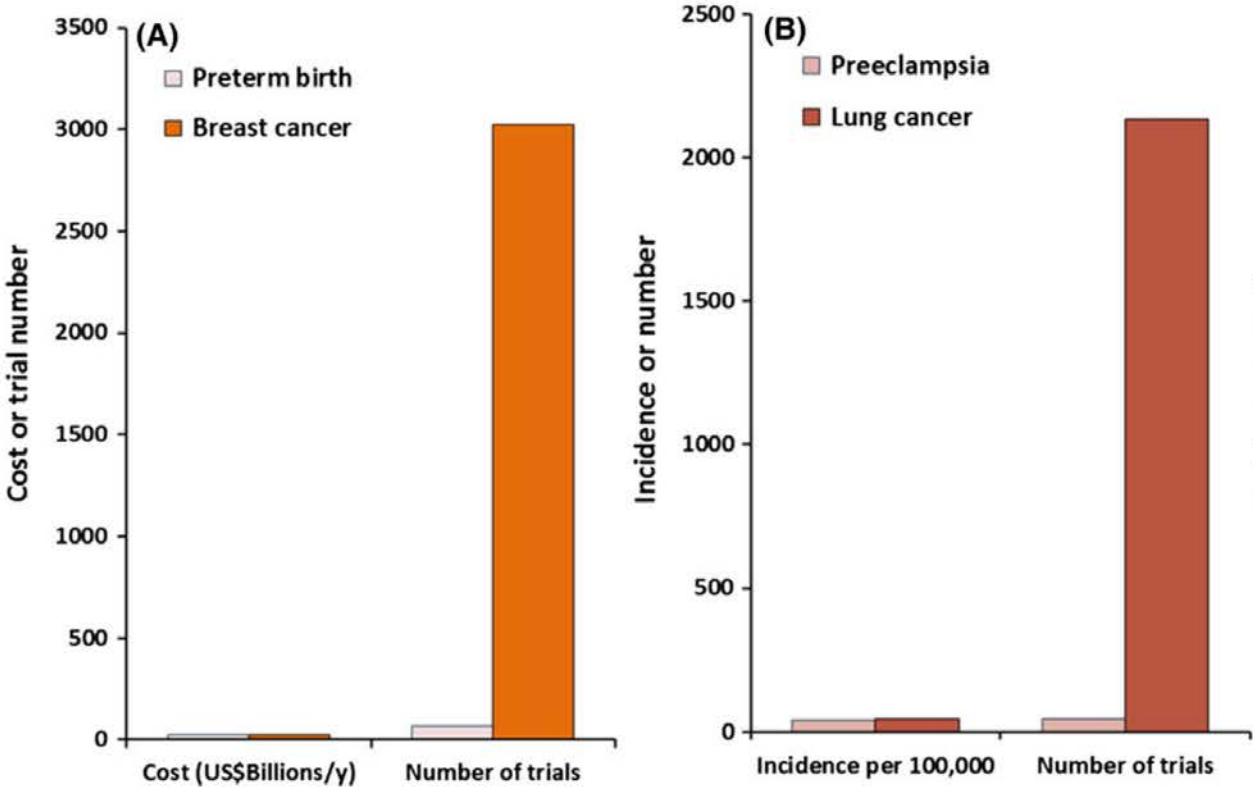

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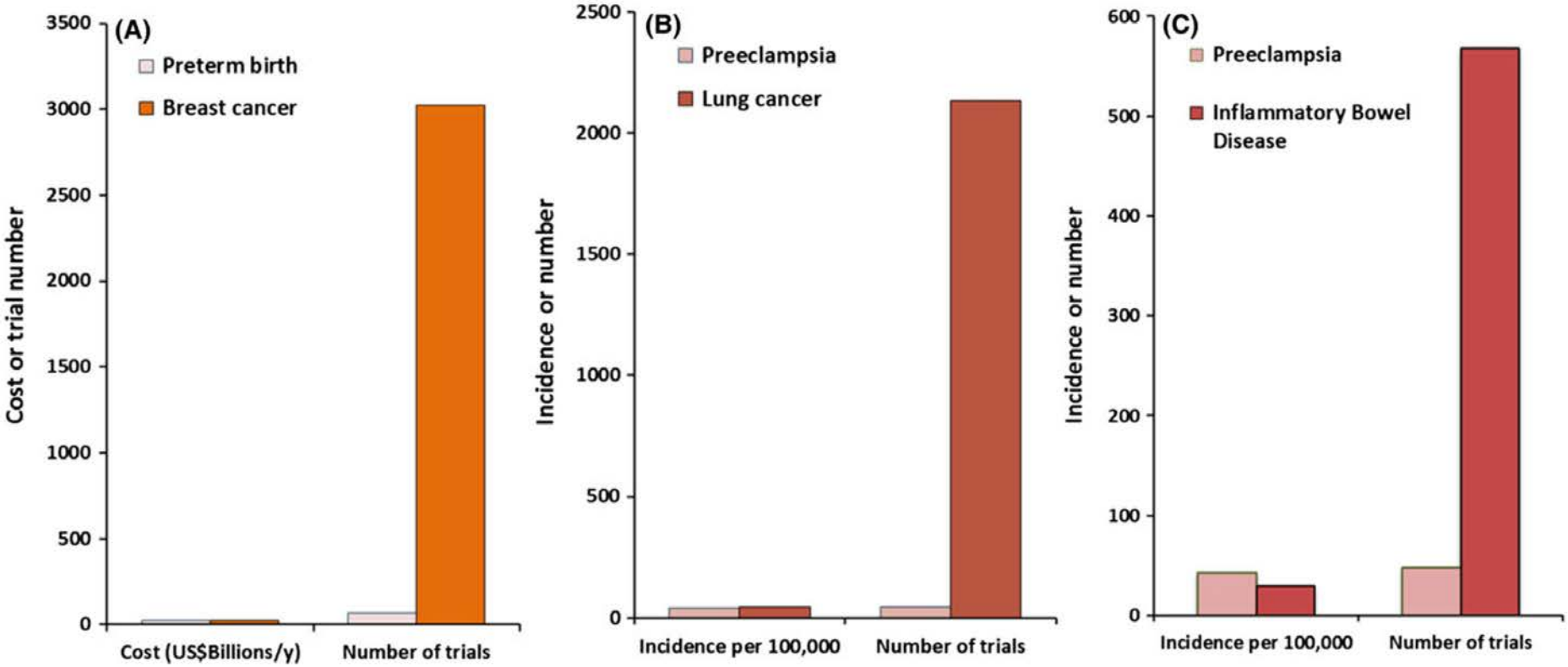
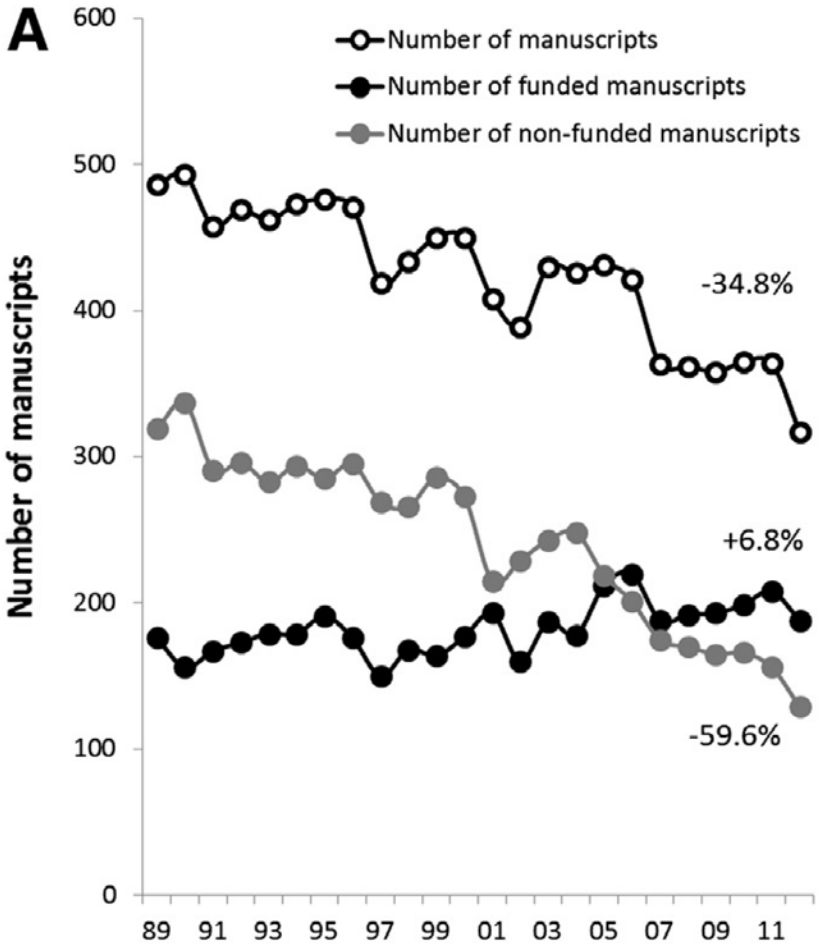


External funding of obstetrical publications: citation significance and trends over 2 decades

William S. Vintzileos; Cande V. Ananth, PhD, MPH; Anthony M. Vintzileos, MD



Am J Obstet Gynecol 2013;209:150.e1-6.

Trends in National Institutes of Health Funding for Clinical Trials Registered in ClinicalTrials.gov

Table 2. Trials Registered in ClinicalTrials.gov From 2006 Through 2014 by Year of Trial Start[a]

Year of trial start	Total No. of Trials[b]	Funding Agency, No. (%)[c]			
		National Institutes of Health	Industry	Other US Federal Agency	All Others
2006	9208	1189 (12.9)	4516 (49.0)	229 (2.5)	3397 (36.9)
2007	10275	1035 (10.1)	4950 (48.2)	265 (2.6)	4163 (40.5)
2008	11650	1039 (8.9)	5359 (46.0)	278 (2.4)	5078 (43.6)
2009	12507	1062 (8.5)	5469 (43.7)	300 (2.4)	5807 (46.4)
2010	12903	1062 (8.2)	5325 (41.3)	311 (2.4)	6324 (49.0)
2011	13514	949 (7.0)	5424 (40.1)	304 (2.2)	6955 (51.5)
2012	13909	935 (6.7)	5135 (36.9)	290 (2.1)	7668 (55.1)
2013	14221	951 (6.7)	5017 (35.3)	306 (2.2)	8084 (56.8)
2014	14618	873 (6.0)	5274 (36.1)	292 (2.0)	8295 (56.7)
% Difference (95% CI) [d,e]	-	-6.9 (-7.7 to -6.2)	-13.0 (-14.2 to -11.7)	-0.5(-0.1 to 0)[f]	19.9 (18.6 to 21.1)
Absolute difference, No. (%)[e]	5410 (58.8)	-316 (-26.6)	758 (16.8)	63 (27.5)	4898 (144.2)

[a] Data as of June 26, 2015.

[b] One trial may have more than 1 funding source.

[c] Unless otherwise indicated.

[d] Comparisons yielded *P* values of <.001 unless otherwise indicated.

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Ehrhardt et al. JAMA 2015;314:2566-7

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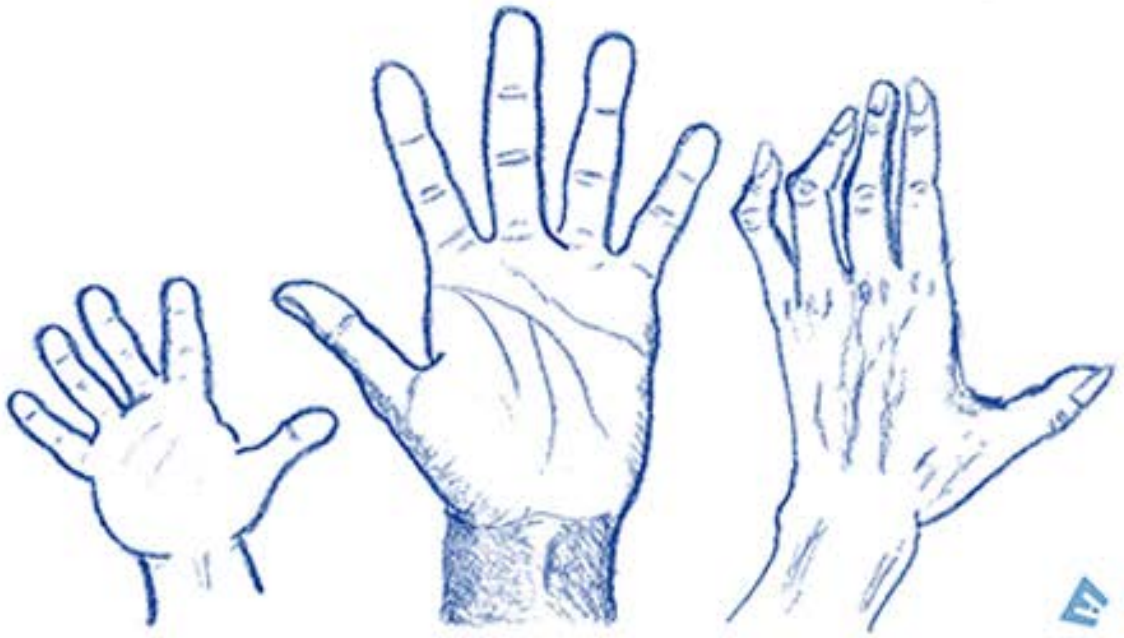
NIH to balance sex in cell and animal studies

Janine A. Clayton and **Francis S. Collins** unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

National Institutes of Health
Turning Discovery Into Health

Inclusion Across the Lifespan



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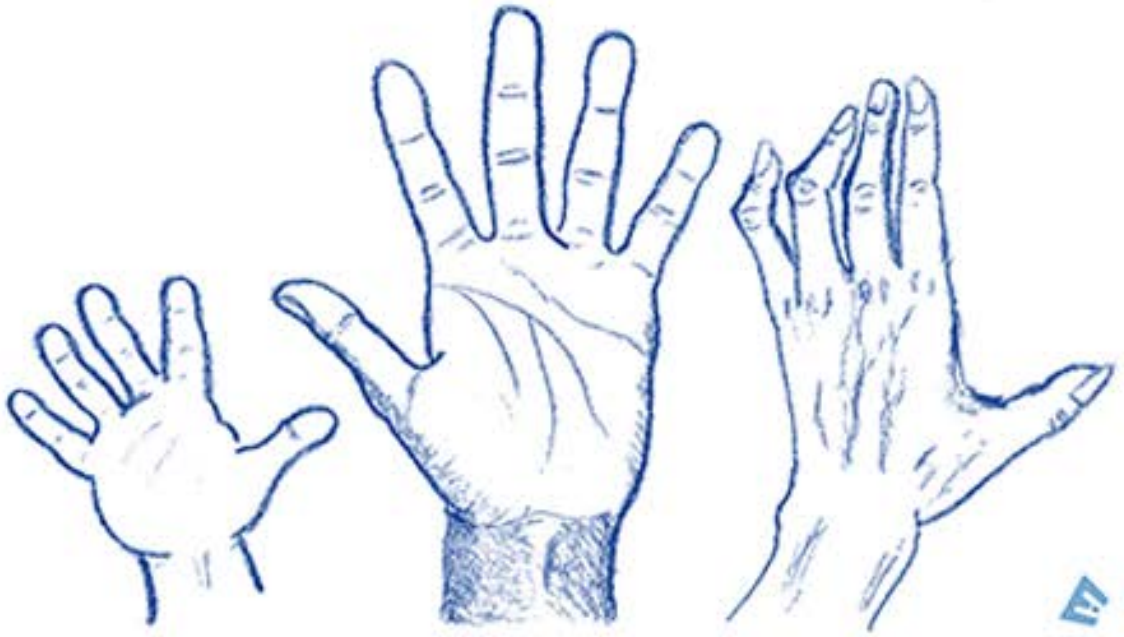

Burden in Pregnancy

- Regulatory
- Paternalistic attitudes (“vulnerability”)
- Lukewarm interest from industry
- Reliance on governmental funding
- Limited researchers

Burden in Pregnancy

- Overemphasize risk to fetus & underemphasize risk of lack of evidence
- Burden of IND and IDE in pregnancy
- IRBs' limited expertise in pregnancy
- No good in-vivo model of placenta
- Reporting of adverse events

Impact

- Discouraging physician scientists
- Using treatments and interventions without evidence
- Preterm birth remains a problem
- Rising maternal mortality and morbidity
- Health disparity

Burden of Tocolytic Trials

- Dose finding studies
- Inclusion criteria different from clinical practice
- Placebo
- Long term outcome
- Two confirmatory trials

Regulatory and methodologic challenges to tocolytic development

TM Goodwin

University of Southern California, Women's and Children's Hospital, Los Angeles, CA, USA
Correspondence: Prof TM Goodwin, University of Southern California, Women's and Children's Hospital, 1240 North Mission Road, Room 5K-40, Los Angeles, CA 90033, USA. Email tgoodwin@usc.edu

Accepted 8 September 2006.

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Accepted 8 September 2006.

4. An increased cooperative effort with regulatory agencies is needed. Several of the problems facing tocolytic development cannot be solved without a significant input from the FDA. It is fair to ask if FDA bears responsibility in part for the fact that there is no approved agent for tocolysis in the USA? Two of the three principal goals for the FDA Modernization Act of 1997 were intended to move the agency from an adversarial culture *vis a vis* industry and investigators to a cooperative one.[11] The FDA should convene a summit meeting on methods for tocolytic phase III development. Such a meeting has been agreed to in principle and is urgently needed.

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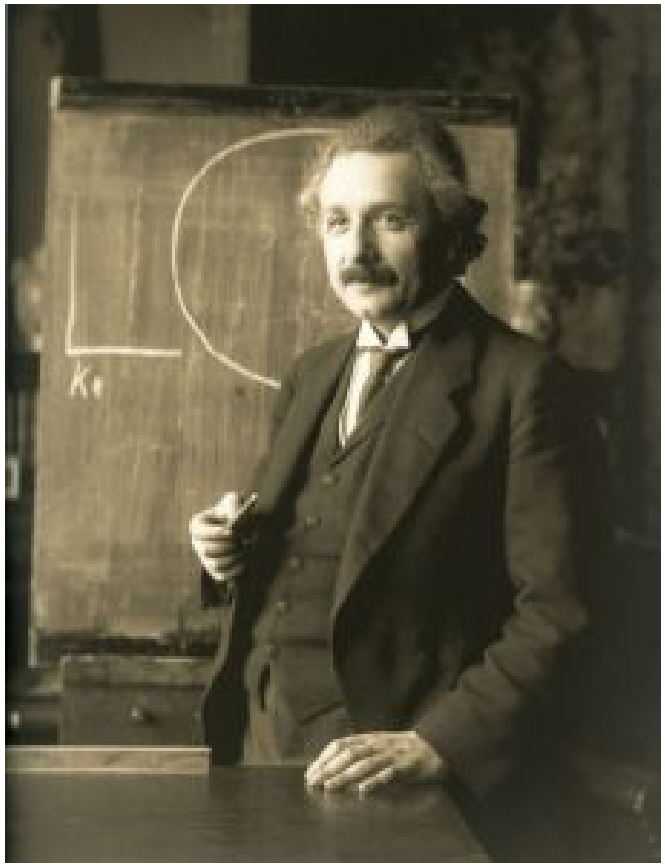
5. Enactment of a 'Best Pharmaceuticals for Pregnant Mothers Act', similar to the Best Pharmaceuticals For Children Act. The status of pregnant women, as 'pharmaceutical orphans' can only be partially addressed by clinician scientists. There must be recognition and a consensus that safe and efficient development of drugs for use during

Burden of Prevention of Postpartum Hemorrhage

- IND
- Wait until cord clamping
- Breastfeeding
- Neonatal examination
- Creeping clinical practice



If we knew what we were doing, it would not be called research, would it?