Using statistics to fight cancer: Examples from Don Berry's career

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Dana Farber Cancer Institute
and Harvard School of Public Health

ENAR, March 2010

Celebrating

21
at last!

A big break for Berry came in 1990, when he was invited to join Cancer and Leukemia Group B (CALGB). It's one of the country's 10 cooperative groups: multi-institutional collaborations on large-scale cancer clinical trials. Berry would be the lead statistician for CALGB's breast cancer studies. He was not greeted warmly.

"I objected rather strenuously," recalls I. Craig Henderson, a breast oncologist at the University of California, San Francisco, who had heard that Bayesians were "loosey-goosey" in adhering to the rules.

CREDIT: BARRY G. SMITH

Improved Outcomes From Adding Sequential Paclitaxel but Not From Escalating Doxorubicin Dose in an Adjuvant Chemotherapy Regimen for Patients With Node-Positive Primary Breast Cancer

By I. Craig Henderson, Donald A. Berry, George D. Demetri, Constance T. Cirrincione, Lori J. Goldstein, Silvana Martino, James N. Ingle, M. Robert Cooper, Daniel F. Hayes, Katherine H. Tkaczuk, Gini Fleming, James F. Holland, David B. Duggan, John T. Carpenter, Emil Frei III, Richard L. Schilsky, William C. Wood, Hyman B. Muss, and Larry Norton

Purpose: **This study was designed to determine whether increasing the dose of doxorubicin in or adding paclitaxel to a standard adjuvant chemotherapy regimen for breast cancer patients would prolong time to recurrence and survival.**

Patients and Methods: **After surgical treatment, 3,121 women with operable breast cancer and involved lymph nodes were randomly assigned to receive a combination of cyclophosphamide (C), 600 mg/m^2, with one of three doses of doxorubicin (A), 60, 75, or 90 mg/m^2, for four cycles followed by either no further therapy or four cycles of paclitaxel at 175 mg/m^2. Tamoxifen was given to 94% of patients with hormone receptor–positive tumors.**

Results: **There was no evidence of a doxorubicin dose effect. At 5 years, disease-free survival was 69%, 66%, and 67% for patients randomly assigned to 60, 75, and 90 mg/m^2, respectively. The hazard reductions from adding paclitaxel to CA were 17% for recurrence (adjusted Wald χ^2 $P = .0023$; unadjusted Wilcoxon $P = .0011$) and 18% for death (adjusted $P = .0064$; unadjusted $P = .0098$). At 5 years, the disease-free survival (± SE) was 65% (± 1) and 70% (± 1), and overall survival was 77% (± 1) and 80% (± 1) after CA alone or CA plus paclitaxel, respectively. The effects of adding paclitaxel were not significantly different in subsets defined by the protocol, but in an unplanned subset analysis, the hazard ratio of CA plus paclitaxel versus CA alone was 0.72 (95% confidence interval, 0.59 to 0.86) for those with estrogen receptor–negative tumors and only 0.91 (95% confidence interval, 0.78 to 1.07) for patients with estrogen receptor–positive tumors, almost all of whom received adjuvant tamoxifen. The additional toxicity from adding four cycles of paclitaxel was generally modest.**

Conclusion: **The addition of four cycles of paclitaxel after the completion of a standard course of CA improves the disease-free and overall survival of patients with early breast cancer.**

J Clin Oncol 21:976-983.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

HER2 and Response to Paclitaxel in Node-Positive Breast Cancer

Daniel F. Hayes, M.D., Ann D. Thor, M.D., Lynn G. Dressler, Dr.Ph., Donald Weaver, M.D., Susan Edgerton, M.A., David Cowan, B.A., Gloria Broadwater, M.S., Lori J. Goldstein, M.D., Silvana Martino, D.O., James N. Ingle, M.D., I. Craig Henderson, M.D., Larry Norton, M.D., Eric P. Winer, M.D., Clifford A. Hudis, M.D., Matthew J. Ellis, M.B., Ph.D., and Donald A. Berry, Ph.D., for the Cancer and Leukemia Group B (CALGB) Investigators*

FOUR SHORT STORIES

EPISODE 1: MAY I HAVE A LOOK?

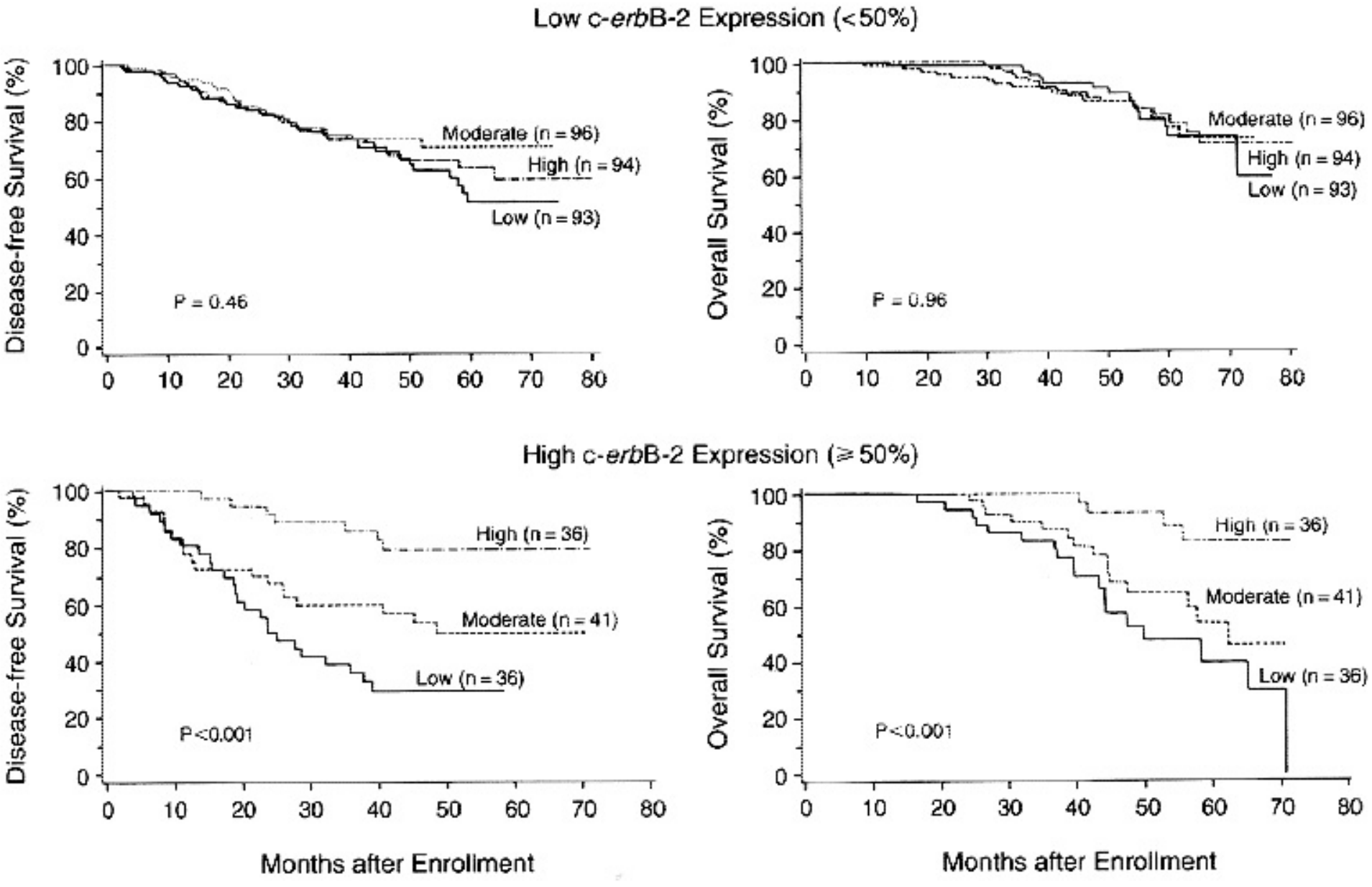
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

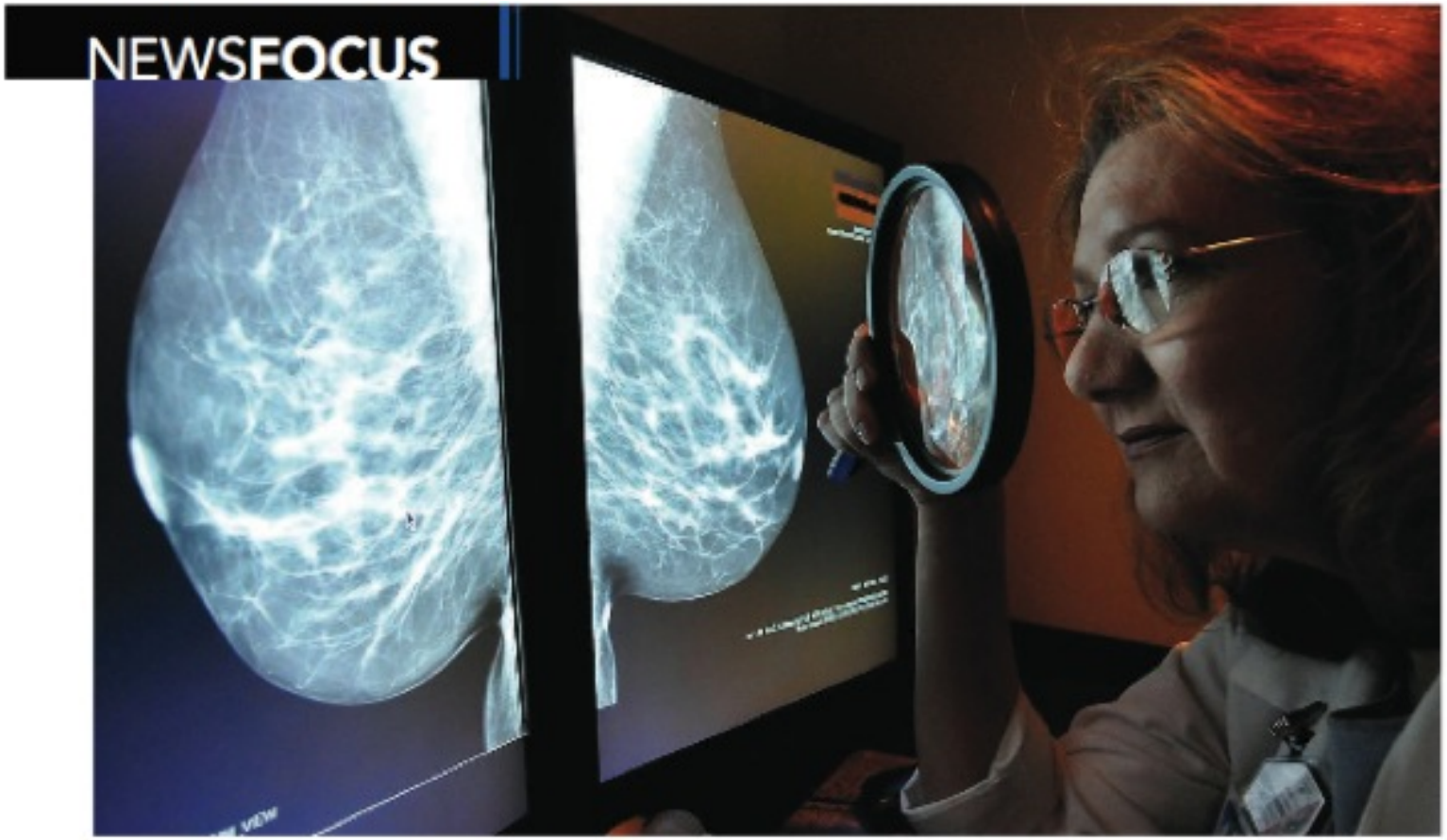
Previous Volume 330:1260-1266 May 5, 1994 Number 18 Next

c-erbB-2 Expression and Response to Adjuvant Therapy in Women with Node-Positive Early Breast Cancer

Hyman B. Muss, Ann D. Thor, Donald A. Berry, Timothy Kute, Edison T. Liu, Frederick Koerner, Constance T. Cirrincione, Daniel R. Budman, William C. Wood, Maurice Barcos, and I. Craig Henderson


Low c-erbB-2 Expression (<50%)
Disease-free Survival (%)
Moderate (n = 96)
High (n = 94)
Low (n = 93)
P = 0.46
Overall Survival (%)
Moderate (n = 96)
High (n = 94)
Low (n = 93)
P = 0.96
High c-erbB-2 Expression (≥ 50%)
Disease-free Survival (%)
High (n = 36)
Moderate (n = 41)
Low (n = 36)
P<0.001
Months after Enrollment
Overall Survival (%)
High (n = 36)
Moderate (n = 41)
Low (n = 36)
P<0.001
Months after Enrollment

EPISODE 2: THE TRUTH



Brawling Over Mammography

A scientific study of the benefits and harms of screening women in their 40s got buried by politics

The Obama Administration is a self-described champion of science. But it was put on the spot last fall when it received a scientific report that questioned the value of the American College of Radiology, Daniel Kopans of Massachusetts General Hospital in Boston, was less restrained. He circulated a critique saying that the sponsor of the new

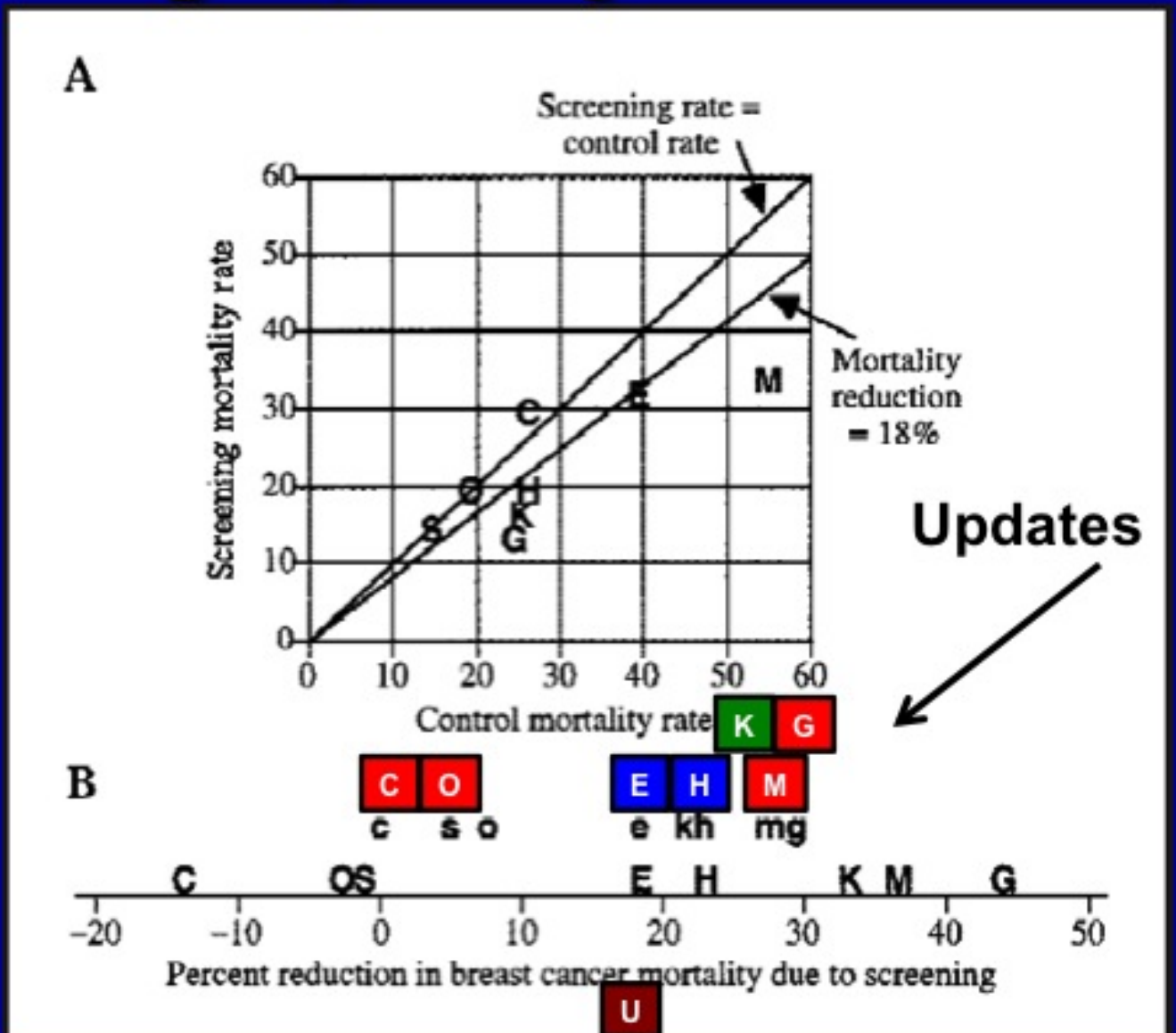
Researchers who had worked on the USPSTF guidelines were disappointed that their analysis was being dismissed out of hand. "Politics got in the way of the science and the best public health practice," says Jeanne Mandelblatt, an M.D.-epidemiologist at Georgetown University in Washington, D.C., and first author of an analysis for USPSTF by six groups that compared models to find the best screening strategy. "It was very unfortunate," adds Heidi Nelson, an M.D.-epidemiologist at the Oregon Health & Science University in Portland, who led a separate team that gathered evidence for USPSTF.

1998 National Institutes of Health Consensus Development Conference Statement: breast cancer screening for women ages 40–49, January 21–23, 1997.
1998 JNCI Article, 1.37 Days

2002 PDQ (Physician's Data Query) Screening and Prevention Editorial Board $\longrightarrow$ Testimony at Senate Hearing

2009 Cisnet $\longrightarrow$ USPTF Report "against" mammography

Fig. 1, Berry JNCI 1998



S

CLINICAL GUIDELINES | Annals of Internal Medicine

Effects of Mammography Screening Under Different Screening Schedules: Model Estimates of Potential Benefits and Harms

Jeanne S. Mandelblatt, MD, MPH; Kathleen A. Cronin, PhD; Stephanie Bailey, PhD; Donald A. Berry, PhD; Harry J. de Koning, MD, PhD; Gerrit Draisma, PhD; Hui Huang, MS; Sandra J. Lee, DSc; Mark Munsell, MS; Sylvia K. Plevritis, PhD; Peter Ravdin, MD, PhD; Clyde B. Schechter, MD, MA; Bronislava Sigal, PhD; Michael A. Stoto, PhD; Natasha K. Stout, PhD; Nicolien T. van Ravesteyn, MSc; John Venier, MS; Marvin Zelen, PhD; and Eric J. Feuer, PhD; for the Breast Cancer Working Group of the Cancer Intervention and Surveillance Modeling Network (CISNET)*

Background: Despite trials of mammography and widespread use, optimal screening policy is controversial.

Objective: To evaluate U.S. breast cancer screening strategies.

Design: 6 models using common data elements.

Data Sources: National data on age-specific incidence, competing mortality, mammography characteristics, and treatment effects.

Target Population: A contemporary population cohort.

Time Horizon: Lifetime.

Perspective: Societal.

Interventions: 20 screening strategies with varying initiation and cessation ages applied annually or biennially.

Outcome Measures: Number of mammograms, reduction in deaths from breast cancer or life-years gained (vs. no screening), false-positive results, unnecessary biopsies, and overdiagnosis.

Results of Base-Case Analysis: The 6 models produced consistent rankings of screening strategies. Screening biennially maintained an average of 81% (range across strategies and models, 67% to 99%) of the benefit of annual screening with almost half the number of false-positive results. Screening biennially from ages 50 to 69 years achieved a median 16.5% (range, 15% to 23%) reduction in breast cancer deaths versus no screening. Initiating biennial screening at age 40 years (vs. 50 years) reduced mortality by an additional 3% (range, 1% to 6%), consumed more resources, and yielded more false-positive results. Biennial screening after age 69 years yielded some additional mortality reduction in all models, but overdiagnosis increased most substantially at older ages.

Results of Sensitivity Analysis: Varying test sensitivity or treatment patterns did not change conclusions.

Limitation: Results do not include morbidity from false-positive results, patient knowledge of earlier diagnosis, or unnecessary treatment.

Conclusion: Biennial screening achieves most of the benefit of annual screening with less harm. Decisions about the best strategy depend on program and individual objectives and the weight placed on benefits, harms, and resource considerations.

Primary Funding Source: National Cancer Institute.

For author affiliations, see end of text.

British Journal of Cancer (2008) 98, 1729 – 1730

www.bjcancer.com

Editorial

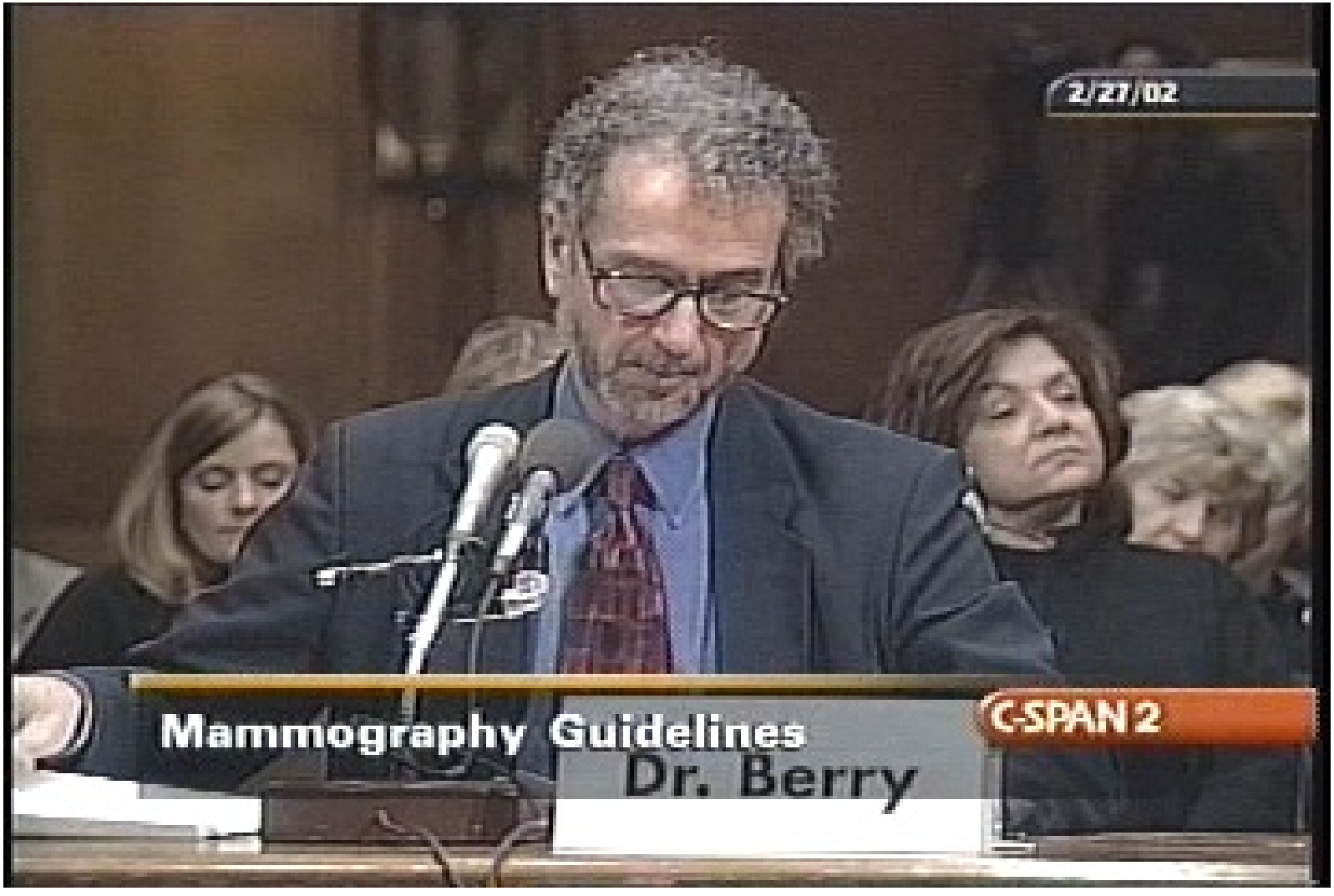
The screening mammography paradox: better when found, perhaps better not to find

DA Berry[1]

[1]*Division of Quantitative Statistics, Department of Biostatistics, University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Box 447, Houston, TX 77030, USA*

British Journal of Cancer (2008) **98,** 1729 – 1730. doi:10.1038/sj.bjc.6604349 www.bjcancer.com
Published online 27 May 2008

2002 Senate Hearing



What should we tell women? The short answer is “the truth”.

Screening for Breast Cancer Over the Age of 80

JOURNAL OF CLINICAL ONCOLOGY

CORRESPONDENCE

Flawed Inferences About Screening Mammography's Benefit Based on Observational Data

TO THE EDITOR: A recent article by Badgwell et al[1] finds that among breast cancer patients at least 80 years of age, the 5-year breast cancer–specific survival was 82% among women who were nonusers of screening mammography, as opposed to 88% among those who were irregular users of screening and 94% among regular users. The investigators are cautious about the implications of this observation: "Our findings add to the accumulating evidence that the use of regular mammography may be beneficial for older women."[1(p6)] However, they are not cautious enough. Observations such as theirs are expected with any screening program and cannot address benefit.

The authors point out that their study was subject to a healthy-person bias. While true, the real culprits are lead-time and length biases, which they do not mention. These biases are elementary and fundamental in cancer epidemiology. But they seem to have been unknown also to the Journal's editors who handled the manuscript—had they understood them, they could not have accepted the manuscript for publication.

Lead-time bias is the easier of the two to understand. A woman whose cancer is detected *n* years early through breast cancer screening will live *n* years longer after her tumor is discovered. The pure bias of *n* years adds to the survival time of all women whose tumors were detected by screening. Because of the heterogeneity of the disease, tend to be less aggressive (especially when detected mammographically) than those found in younger women.

Lead-time and length biases give rise to the stage shift associated with screening mammography that is always observed in studies such as that of Badgwell et al.[1]

Quantifying these biases precisely is difficult, if not impossible. This is why investigators in several countries have conducted randomized screening trials. None of the trials included women in their 80s. The oldest women included in the screening trials (in Sweden) were in their 70s. Because the sample size was small, the results were far from conclusive. But women in this subset who were not screened actually had lower breast cancer mortality than those who were screened. In sum, credible evidence of a beneficial effect of breast cancer screening for older women does not exist, but there is solid evidence of harms.

The article by Badgwell et al[1] might have had minimal impact on women were it not for the news media picking up the story. Coverage was predictable and considerable. The media painted stronger conclusions than the authors may have intended. The American Society of Clinical Oncology fanned the flames with its totally inaccurate and misleading press release entitled, "Women 80 and Older Benefit from Mammography, but Few Are Screened."[2]

The *Journal of Clinical Oncology* erred in publishing this article. It was a disservice to women, young as well as old. Such publication reveals a seriously defective editorial process at the journal.

Donald A. Berry

Division of Quantitative Sciences, The University of Texas M.D. Anderson Cancer Center, Houston, TX

Screening for Breast Cancer Over the Age of 80

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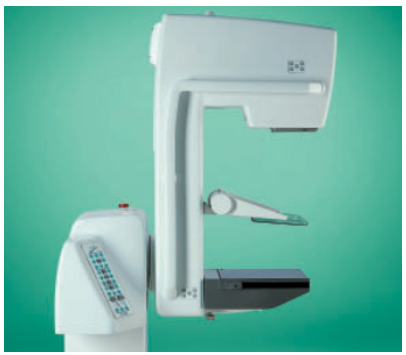
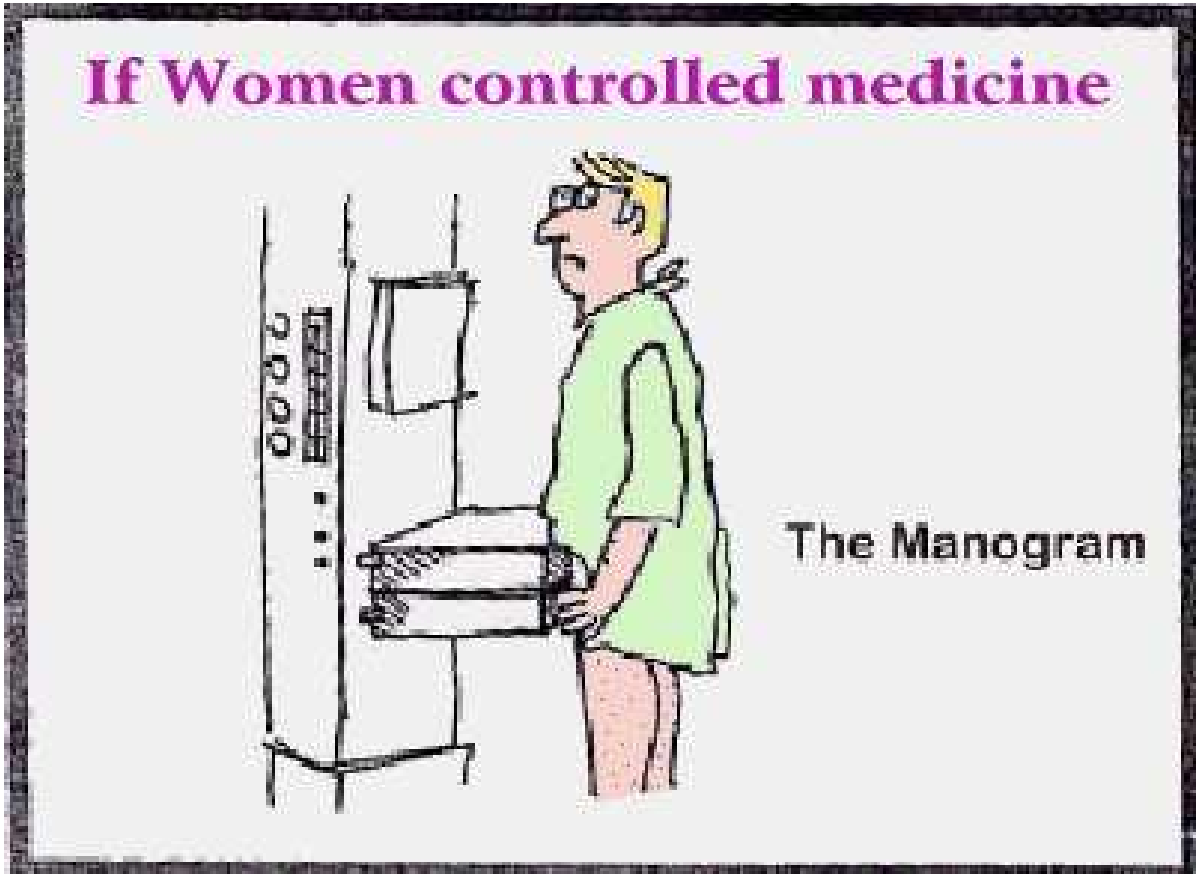



If Women controlled medicine
The Manogram

EPISODE 3: THE DOG THAT DID NOT BARK

Living With the BRCA Gene: One Family's Story

Generations of the Price family have been affected by a mutation in the BRCA1 gene that significantly raises the risk of breast and ovarian cancer. A parent who carries the defective gene has a 50 percent chance of passing it on to his or her children. In 2002, Christie Veale became the first family member to get a DNA test that revealed she had inherited the mutation from her mother. As many of her relatives followed, they have made different choices about how to manage their genetic predisposition to the life-threatening condition.

Robert Milton Price
Died of colon cancer at age 50.

Two of Robert and Eleanor's sisters died of breast cancer. Another sister died of ovarian cancer.

Eleanor Price Veith, 87
Has not been tested for the gene, but is assumed to be positive because her daughter has it. Ovarian cancer was diagnosed.

Robert Neville Price
Died of pancreatic cancer. One of his daughters died of breast cancer.

Rosalyn Price Pierce
Had never been tested for the gene, but must have passed it to her daughter. First developed breast cancer at age 34. Died of breast cancer in July at age 67.

Janice Price Brown
Had never been tested for the gene, but must have passed it to her daughters. Ovarian and breast cancer were first diagnosed at age 33. Died of breast cancer at age 57 in 2001.

Joan Veith Lindner, 64
Learned she had breast cancer at age 48, underwent chemotherapy and had her breasts and ovaries removed. She later tested positive for the gene.

"When I tested positive I knew my daughters needed to be tested as well."

Gloria Veith Spurlock, 59
Has not been tested.

"There's no real need to know because it is a situation where we would just continue to take care of ourselves extremely well."

Dana Pierce, 47
Tested negative for the gene.

Brenda Russo, 41
Tested positive for the gene, and had her ovaries removed. Goes for frequent mammograms and M.R.I.'s.

"I know some women have their breasts removed. To me that's a little drastic... I'm not safe from getting cancer, but I'm pretty confident that we would catch it early if we ever did catch it."

Jodi Dembeck, 41
After her sister learned she had cancer, she tested positive for the gene. She gets regular mammograms and is waiting to decide whether to have a fourth child before considering surgery.

"You can have everything taken out and a few cells maybe weren't caught. There's no foolproof way to avoid cancer."

Christie Veale, 39
After breast cancer was diagnosed, she tested positive for the gene. She then had a bilateral mastecomy and later had her ovaries removed.

"I've gotten rid of the areas where it can come. I'd rather be proactive than have something chasing me."

Lori French, 37
Tested negative for the gene.

"When they explained that that means my daughter would not get it either, I was elated."

Deborah Lindner, 33
Tested positive for the gene and had a prophylactic mastectomy this summer at age 33. She is planning to have her ovaries removed before she turns 40.

"I just feel really happy that I don't have to worry about this anymore."

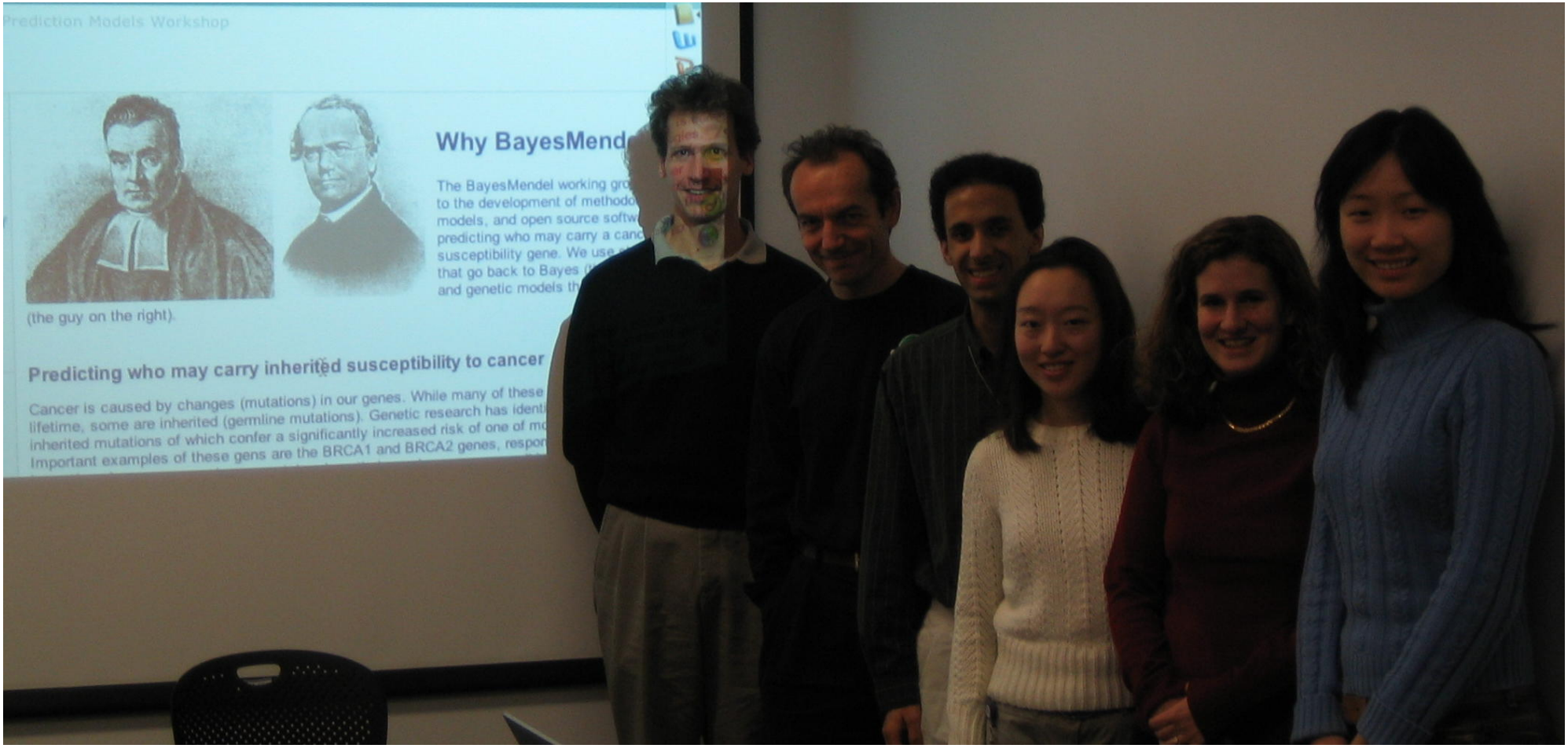
Lisa Spurlock's brother has not been tested for the gene. He requested that his name and picture be withheld because of the potential for discrimination based on his genetic risk.

Lisa Spurlock, 24
Has not been tested.

"Since cancer runs in my family it makes me more aware of my lifestyle. I eat a lot of raw fruits and vegetables and try to be healthier."

THE NEW YORK TIMES

BayesMendel Group



Bayes, Mendel, Iversen, Parmigiani, Katki, Chen, Klein, Wang

Andy, there is no BRCA3

BRCAPRO Validation, Sensitivity of Genetic Testing of *BRCA1/BRCA2*, and Prevalence of Other Breast Cancer Susceptibility Genes

By Donald A. Berry, Edwin S. Iversen, Jr, Daniel F. Gudbjartsson, Elaine H. Hiller, Judy E. Garber, Beth N. Peshkin, Caryn Lerman, Patrice Watson, Henry T. Lynch, Susan G. Hilsenbeck, Wendy S. Rubinstein, Kevin S. Hughes, and Giovanni Parmigiani

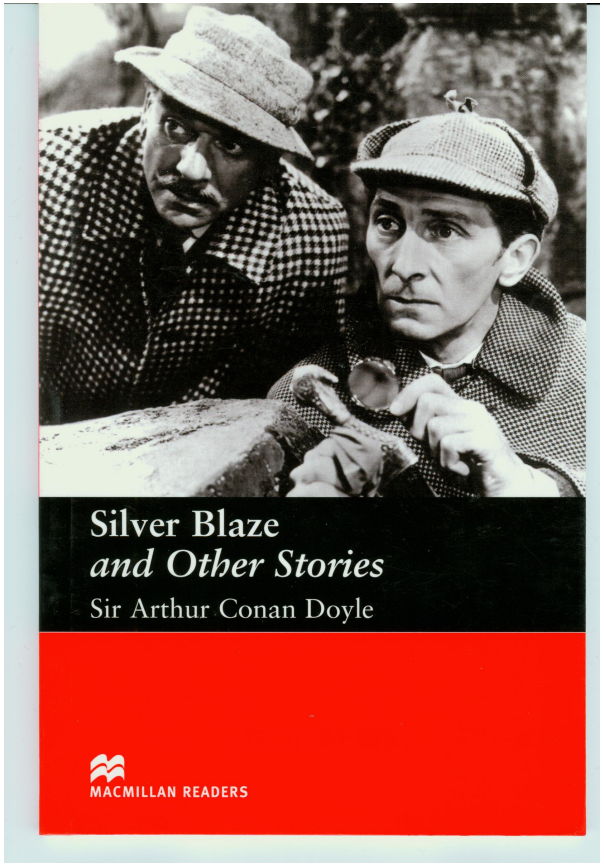
Purpose: **To compare genetic test results for deleterious mutations of *BRCA1* and *BRCA2* with estimated probabilities of carrying such mutations; to assess sensitivity of genetic testing; and to assess the relevance of other susceptibility genes in familial breast and ovarian cancer.**

Patients and Methods: **Data analyzed were from six high-risk genetic counseling clinics and concern individuals from families for which at least one member was tested for mutations at *BRCA1* and *BRCA2*. Predictions of genetic predisposition to breast and ovarian cancer for 301 individuals were made using BRCAPRO, a statistical model and software using Mendelian genetics and Bayesian updating. Model predictions were compared with the results of genetic testing.**

Results: **Among the test individuals, 126 were Ashkenazi Jewish, three were male subjects, 243 had breast cancer, 49 had ovarian cancer, 34 were unaffected, and 139 tested positive for *BRCA1* mutations and 29 for *BRCA2* mutations. BRCAPRO performed well: for the 150 probands with the smallest BRCAPRO carrier probabilities (average, 29.0%), the proportion testing positive was 32.7%; for the 151 probands with the largest carrier probabilities (average, 95.2%), 78.8% tested positive. Genetic testing sensitivity was estimated to be at least 85%, with false-negatives including mutations of susceptibility genes heretofore unknown.**

Conclusion: **BRCAPRO is an accurate counseling tool for determining the probability of carrying mutations of *BRCA1* and *BRCA2*. Genetic testing for *BRCA1* and *BRCA2* is highly sensitive, missing an estimated 15% of mutations. In the populations studied, breast cancer susceptibility genes other than *BRCA1* and *BRCA2* either do not exist, are rare, or are associated with low disease penetrance.**

J Clin Oncol 20:2701-2712. © 2002 by American Society of Clinical Oncology.



"Is there any point to which you would wish to draw my attention?"

"To the curious incident of the dog in the night-time."

"The dog did nothing in the night-time."

"That was the curious incident," remarked Sherlock Holmes.

The only person at whom the stable dog would not bark warnings was the dog's owner. Hence, the dog's silence indicated that the only one who could have entered the stable and killed the horse, was the dog's owner.

EPISODE 4: THE SPIES

INVESTIGATION OF SERIAL STUDIES TO PREDICT YOUR
THERAPEUTIC RESPONSE WITH IMAGING AND MOLECULAR ANALYSIS

Paradigm shifts:

- adaptivity
- more than one company in the same trial
- Bayesian design

Houston, 2010

These are my predictions.
And of course, just like all probabilistic predictions, they could be wrong .....

Houston, 2010

These are my predictions.
And of course, just like all probabilistic predictions, they could be wrong .....

though that hasn't happened to me yet.