

# CCEB Newsletter



*CCEB experts shed light on the reported drop in the breast cancer rate as well as the implications of the Women's Health Initiative.*

A Quarterly Newsletter

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## Feature Article:

Drs. Norman and Ellenberg provide insight into the drop in the breast cancer rate and discuss hormone replacement therapy, responses to menopausal symptoms, and the implications of the Women's Health Initiative **Page 1**

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## A Q&A on the breast cancer rate decline, the Women's Health Initiative, and menopause

**A**t the 29<sup>th</sup> Annual San Antonio Breast Cancer Symposium, December 14-17, 2006, researchers from the M.D. Anderson Cancer Center in Houston reported a dramatic 7% decline in breast cancer incidence in 2003. (Ravdin P, Cronin K, Howlander N, et al. A Sharp Decrease in Breast Cancer Incidence in the United States in 2003. Proceedings from the 2006 annual San Antonio Breast Cancer Symposium (SABCS). San Antonio, Texas. Oral presentation December 14, 2006. Abstract 5.) This represented the first significant decrease in breast cancer rates, which was seen by some as especially remarkable given the small but steady annual increase in breast cancer rates

since 1945. The researchers speculated that the substantial decline in the use of hormone replacement therapy (HRT) among postmenopausal women following the cessation of the Women's Health Initiative in 2002, which indicated that HRT raises the breast cancer risk, may be at the root of such findings.

An article by Gina Kolata that appeared in *The New York Times* on the 15<sup>th</sup> of December briefly summarized these findings and also cited the results of a separate study in California that appeared to support the conclusions of the M.D. Anderson team (Clarke CA, Glaser SL, Uratsu CS, Selby JV, Kushi LH, Herrinton LJ. Recent declines in hormone therapy utilization and breast cancer incidence: clinical and population-based evidence. *J Clin Oncol.* 2006 Nov 20;24(33):e49-50).

In our feature article, Sandra Norman, PhD, Research Associate Professor of Epidemiology, Senior

Fellow, Leonard Davis Institute of Health Economics, Fellow, Institute on Aging, Member, Abramson Cancer Center, University of Pennsylvania SOM, and Senior Scholar in the CCEB and Susan Ellenberg, PhD, Associate Dean for Clinical Research, University of Pennsylvania SOM, Professor of Biostatistics at HUP, University of Pennsylvania, SOM, and Senior Scholar, Biostatistics, CCEB, who was also quoted in *The New York Times* article, will elaborate on these findings and provide an update on the status of HRT.

**Q:** *Is it fair to say that the appreciable drop in breast cancer incidence in one year, four years ago, is positive news but insufficient, in and of itself, to determine if the overall trend is reversing?*

**SN:** It is fair to say

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# Faculty Profile:

*Scarlett Bellamy, ScD, focuses on community-based projects and health disparities*



**Scarlett Bellamy, ScD, Assistant Professor of Biostatistics in the CCEB**

**S**carlett Bellamy, ScD, grew up on a farm in North Carolina. Introduced to the notion of hard work by the lifestyle, Scarlett developed an early interest in medicine that she maintained throughout her childhood. Also during her formative years, Scarlett would spend several weeks during the

summer with her aunt who taught college algebra at North Carolina Central University and who challenged her to learn the information she was presenting to her summer school students. These early summer experiences engendered and nurtured a passion for mathematics, especially since girls were not expected to excel in math and science.

When she started her undergraduate career at Hampton University in Hampton, VA, Scarlett intended to be pre-med. During the summer after her sophomore year, Scarlett, along with friend and classmate Knashawn Morales, ScD, Assistant Professor of Biostatistics at HUP, University of Pennsylvania SOM, Senior Scholar, Biostatistics in the CCEB, were required to seek summer research experiences outside of Hampton to foster their interest in graduate training and further their career plans. They applied to such a program at the University of North Carolina in Chapel Hill and were matched with a mentor who happened to be a biostatistician. Scarlett found an appeal in the applied nature of biostatistics. As she entered her junior year at Hampton, the tangible applications of statistics and math held sway, as Scarlett decided not to pursue medical school. She graduated with a BA in mathematics in 1995. But majoring in math was not a decision against medicine, per se. In fact, she thought that the best way to marry her medical and mathematical interests would be to build on her summer experiences at UNC and pursue her education in biostatistics. Scarlett earned an ScM in biostatistics at Harvard University in 1997. During this period, she served as a statistical consultant in the Department of Biostatistics at the Harvard School of Public Health

and as a statistical consultant in the Visiting Clerkship Program in the Harvard Medical School Faculty Development and Diversity Program. Although she initially thought that she might return to North Carolina for doctoral studies, Scarlett elected to stay at Harvard, where she completed her ScD in 2001. From 1996 to 2000, Dr. Bellamy was a graduate assistant in the Summer Program in Biostatistics in the Harvard School of Public Health and also a guest lecturer in the Health Policy Summer Program there. As a graduate student, she also gained practical experience by serving as a statistical consultant in the East Boston Asthma Study from 1999 to 2001.

In 2001, Dr. Bellamy accepted the position of Assistant Professor of Biostatistics in the Department of Biostatistics and Epidemiology in the University of Pennsylvania SOM. She is also a Senior Scholar in the CCEB. Dr. Bellamy is a member of the Eastern North American Region (ENAR) of the International Biometrics Society, and the American Statistical Association. She won an ENAR Student Paper Award in 2002, and was appointed Chair of ENAR's Regional Advisory Board (2005-2007). Earlier this year, she was nominated for a Lindback Career Enhancement for Minority Junior Faculty grant, which was pending at press time.

In her research, Dr. Bellamy focuses on problems related to the design and analysis of group- or cluster-randomized trials. She primarily applies this methodology to community-based research projects and those that address health disparities for various clinical and behavioral health outcomes. She has engaged in collaborative projects on women's reproductive health as well as mental health issues of the elderly. Currently, she is involved in a multicenter cohort study of HIV behavioral risk reduction for African Americans. Most of the behavioral work is related to teaching people at high risk of contracting the disease, particularly people in a relationship with an HIV-positive partner. Dr. Bellamy is also participating in a clustered-by-design study working on the idea of measuring lung impairment over the first 3 to 4 days following lung transplant or acute lung injury. This study offers a different spin on clustered data applications insofar as each person represents his/her own cluster. Instead of modeling a patient's post-

*(Continued on page 4)*

# Faculty Profile:

*John Holmes, PhD, applies medical informatics to epidemiologic research and has developed several computer programs to assist in his work*

**J**ohn H. Holmes, PhD, was born and raised in Cherry Hill, NJ. After graduating high school from Cherry Hill West, John joined the United States Navy where he served in the Hospital Corps from 1969-71. He describes his training as a hospital corpsman as “the last two years of medical school crammed into 14 weeks.” During this period, John learned various skills, such as physical diagnosis, surgical procedures, patient care, and pharmacology. As he characterizes it now, his training as a hospital corpsman provided him with the skills of today’s physician assistants.

During and following his stint in the Navy, John spent nearly four years in Emergency Medicine and Critical Care at Methodist Hospital; while there, he was privileged to work in one of the region’s first cardiac care units. He then worked as a pulmonary technologist in what was then the Pulmonary Disease Section at the Hospital of the University of Pennsylvania. John looks back with particular fondness on his experiences in field studies in occupational medicine, which included trips to Hazleton, PA, to screen beryllium miners for lung disease. However, it was also during this time that John got a chance to work on computer applications in health care, setting the stage for what would become his primary research interest as a faculty member.

While employed at Methodist and HUP, John was studying for

his Bachelor of Arts in Sociology at the University of Pennsylvania. He earned an AB in 1976 and went to work the next year in the Department of Laboratory Medicine at Pennsylvania Hospital, where he worked as a technologist in the hematology, blood bank, and microbiology labs. During his five years there, John continued his studies not in sociology, research, or medicine, but in musicology, intending to pursue graduate study in medieval music performance practice.



**John Holmes, PhD,  
Assistant Professor of  
Medical Informatics in  
Epidemiology in the  
CCEB**

John had had early training and experience as an organist and was interested in medieval history.

The lure of a research career drew John back into the health sciences, and in 1982 he joined the CCEB’s precursor, the Clinical Epidemiology Unit (CEU), at the University of Pennsylvania. He served as Research Coordinator for two of the four faculty members in the Unit at that time. As a coordinator, he was able to apply his health economics, health services research, statistics and medical sociology course knowledge from his undergraduate career. His clinical work as a hospital corpsman also helped him, but so too did the experience in computing that he gained while working in the Pulmo-

nary Disease Section. John set up and ran the first “computer facility” in the CEU, which at that time consisted of two Apple-II+ computers. He developed and taught courses in computing for fellows in the International Clinical Epidemiology Network (INCLEN) training program. John rose to senior research coordinator and then Medical Information Scientist after receiving a Master of Science in Information Systems degree from Drexel University.

In 1996, John earned a PhD from Drexel University in Information Science, where his focus was on the development of new algorithms for knowledge discovery in databases (KDD, or “data mining”) in epidemiologic surveillance. In 2000, Dr. Holmes became a Senior Scholar at the CCEB and joined the Penn Medicine faculty as Assistant Professor of Medical Informatics in Epidemiology at HUP.

Dr. Holmes’s primary research interest is in the application of medical informatics to epidemiologic research. His work on KDD in epidemiologic surveillance focuses on discovering patterns in data that suggest new hypotheses about associations between exposures and outcomes. Dr. Holmes has developed several computer programs to assist with this work, including EpiCS and EpiXCS. These programs use an approach called “evolutionary computation,” in which knowledge is modeled from data using a “survival of the fittest,”

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## From the Director:



Brian L. Strom, MD, MPH

In each issue of the CCEB Newsletter, which serves as a forum for us to keep you informed of activities within the CCEB, we focus on a few members of our faculty, some of the services we provide to faculty, residents, and fellows within UPHS and those external to Penn, and on newsworthy events likely to be of interest.

In this issue, we profile John Holmes and Scarlett Bellamy. John is Assistant Professor of Medical Informatics in Epidemiology and a Senior Scholar in the CCEB. His research focuses on the application of medical informatics to epidemiologic research. Scarlett joined the faculty in 2001 and continues as Assistant Professor of Biostatistics and Senior Scholar in the CCEB. Her methodologic research includes problems related to the design and analysis of group- or cluster-randomized trials. Her applied work centers primarily on community-based and health disparities research.

The feature article in this issue addresses the big drop reported at the end of the year in the breast cancer rate, the Women's Health Initiative, and related topics.

An additional article describes clinical research services provided by CCEB faculty and staff, which include biostatistical support, assistance with study design, and project and data management services. I also would like to remind those interested in clinical research training of our master's and PhD degree programs in epidemiology (<http://www.cceb.upenn.edu/education/epi-degree/>), our master's and PhD degree programs in biostatistics (<http://www.cceb.upenn.edu/education/bio-degree/>), and our Clinical Research Certificate Program (<http://www.cceb.upenn.edu/education/non-degree/certificate.php>). Registration for Certificate Program courses to be offered this summer (intensive, two week courses, meeting daily from July 16 through July 27) is now available via the following registration portal: [http://www.med.upenn.edu/apps/my/epi\\_course](http://www.med.upenn.edu/apps/my/epi_course). Courses available and the times these courses are offered are listed at the following site: <http://www.cceb.upenn.edu/education/non-degree/coursescrtp.php>. Descriptions of these courses can be found at: <http://www.cceb.upenn.edu/education/non-degree/courses.php#credit>.

Finally, I would like to remind you to check our website regularly for announcements and other newsworthy events (<http://www.cceb.upenn.edu/>) and to find potential faculty collaborators (<http://www.cceb.med.upenn.edu/faculty/>). I hope you enjoy the newsletter!

*(Bellamy, continued from page 2)*

trauma trajectory based on lung impairment as measured on a single day, Dr. Bellamy is exploring, along with colleagues from the CCEB (Drs. Jason Christie, Russ Localio, and Bob Gallop), a latent class approach to classify patterns of lung injury responses, over several days following lung transplant or trauma, as a function of other important donor and recipient characteristics.

Additionally, Dr. Bellamy is an active contributor to the training programs within the CCEB. She has co-taught Methods II, a required course for MS and PhD biostatistics students, with Drs. Phyllis Gimotty and Wei-ting Hwang in the past and currently directs

EPID 623 (Applied Survival Analysis), an applied statistical methods course primarily geared towards the MSCE program. Dr. Bellamy also acts as a student/faculty liaison with Dr. Tom Ten Have in facilitating an annual Student Feedback Session with current graduate students in the Biostatistics program. This allows students to anonymously critique their experiences as graduate student trainees as this information is relayed to faculty members in the Division of Biostatistics to further improve the program. Finally, Dr. Bellamy is committed to enhancing the representation of well-qualified professionals from various cultural backgrounds within the field of biostatistics. To that end,

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that this is a provocative finding that merits serious attention. The recent (2/21/07) news article in JNCI helps put the findings into perspective. (McNeil, C. Breast cancer decline mirrors fall in hormone use, spurs both debate and research. JNCI 99: 266-267, 2007). I have framed my answer in terms of criteria used to determine whether there is a cause-effect relationship. These include the strength of the association, biologic plausibility, consistency with other investigations, time sequence, and the strength of the study design.

#### *Strength of the association*

A 7% drop in breast cancer incidence between 2002 and 2003, reported at the San Antonio meeting, for any one year is impressive. However, there have been other years with large changes in breast cancer incidence that were not maintained (e.g., an increase of 7.9% between 1986 and 1987) and years with large changes in incidence that were maintained (an increase between 1980-81 of 6.3%). More yearly incidence data are needed; at least three years of data are needed to see if a trend exists. Reports from cancer registries are always several years behind. The last year of data that we have available is 2003. The National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program is working hard to get the 2004 data ready and projects it should be ready this April.

#### *Biologic plausibility*

Several studies, including a multicenter case-control study of risk factors for breast cancer (the Women's Contraceptive and Reproductive Experiences (CARE) study) that Brian Strom and I led at the Philadelphia site, have found that the increased risk of breast cancer associated with combined estrogen/progestin hormone therapy (CHT) seems limited to current users. Past users showed no increased risk. In our study, among women taking CHT, the odds ratio (OR) for current users (use within the last 6 months) compared to never users was 1.22 (95% CI 0.99 – 1.50) and showed a

duration-response relationship. The OR for past users (last use six or more months ago) compared to never users was 0.76 (0.60-0.97) and this effect appeared to hold regardless of how long hormones had been used before quitting. (Weiss LK et al. Hormone replacement therapy regimens and breast cancer risk. *Obstet Gynecol.* 2002 Dec;100(6):1148-58.)

A collaborative re-analysis of 51 studies of hormone therapy and breast cancer, as well as the more recently reported Million Women Study, also noted similar results, with risk of cancer returning to that of the general population within five years of stopping use. Thus, the effect of stopping hormone therapy theoretically could be seen quickly, although not necessarily as quickly as was seen in the study reported in San Antonio, where effects on incidence appeared within a month of the cessation of the Women's Health Initiative (WHI) trial.

Among the reasons suggested for the lower risk in past users than current users is that hormone therapy promotes the growth of existing hormonally-dependent breast cancers. Without the external hormones, tumor growth is slowed or stopped. If tumor growth is slowed, the incidence rates could go up again, when these tumors have grown sufficiently to be detectable.

The greatest decline in breast cancer incidence from 2000-2003 was observed in women ages 50-69 years with estrogen receptor-positive tumors, which makes sense given the mechanism by which hormone therapy may work.

*[Note: ER+ tumors are sensitive to estrogen circulating in the body. Estrogen stimulates growth of these tumors. ER- tumors are not sensitive to circulating estrogen. Prognosis is actually better for ER+ tumors because a number of drugs can block the stimulating effect of estrogen on tumor growth.]*

#### *Consistency with other investigations*

Two studies were reported recently. One was based on SEER data; the other compared trends in incidence from the Northern California Cancer Registry and trends in hormone use from the Kaiser Permanente Health system. Results were comparable.

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## Faculty News and Notes

Several CCEB faculty have appeared in the news recently. A brief summary dating from December follows in alphabetical order.

**W**illiam C. Holmes, MD, MSCE, Assistant Professor of Medicine, General Internal Medicine, University of Pennsylvania SOM, Assistant Professor of Epidemiology and Senior Scholar in the CCEB, was interviewed for and quoted in the ABC online news article “Would You Condone Torture in War?” The article, which appeared on the 14<sup>th</sup> of February (<http://abcnews.go.com/Technology/story?id=2872770&page=1>), was based on Dr. Holmes’s paper “Abuse of War Zone Detainees: Veterans’ Perceptions of Acceptability,” published in the February issue of *Military Medicine* (Mil Med 2007 Feb;172 (2):175-81).

Dr. Holmes was also interviewed recently for Dr. Dan Gottlieb’s segment on WHYY radio’s *Morning Edition* segment regarding this study. The interview was aired on the 19<sup>th</sup> of March.

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**Kathryn Schmitz, PhD, MPH**, Assistant Professor of Epidemiology, Department of Biostatistics and Epidemiology, University of Pennsylvania SOM, was quoted in the China View on the 26<sup>th</sup> of January ([http://news.xinhuanet.com/english/2007-01/26/content\\_5657627.htm](http://news.xinhuanet.com/english/2007-01/26/content_5657627.htm)) regarding her study on smoking and exercise (Sinner P, Folsom AR, Harnack L, Eberly LE, Schmitz KH. The association of physical activity with lung cancer incidence in a cohort of older women: the Iowa Women’s Health Study. *Cancer Epidemiol Biomarkers Prev.* 2006 Dec;15(12):2359-63.). The full article can be read here: <http://cebp.aacrjournals.org/cgi/content/full/15/12/2359?maxto-show=&HITS=10&hits=10&RESULTFORMAT=&author1=Schmitz+K&searchid=1&FIRSTINDEX=0&fdate=11/1/2006&resourcetype=HWCIT>.

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**Samir Shah, MD**, Senior Scholar, Epidemiology, University of Pennsylvania SOM, Assistant Professor of Epidemiology, and Assistant Professor of Pediatrics at CHOP, was interviewed for *The Philadelphia Inquirer* article “New Questions on Medicines Given to Young,” by Josh Goldstein, published on the 6<sup>th</sup> of

March (<http://www.philly.com/mld/philly/news/16841956.htm>). The article appeared in response to the publication of Dr. Shah’s study, which confirms in the largest-ever US pediatric study that “off-label” drug use is particularly common in hospitalized children. The full article (Shah SS, Hall M, Goodman DM, Feuer P, Sharma V, Fargason C Jr, Hyman D, Jenkins K, White ML, Levy FH, Levin JE, Bertoch D, Slonim AD. Off-label Drug Use in Hospitalized Children. *Arch Pediatr Adolesc Med.* 2007 Mar;161 (3):282-90) can be read here: <http://archpedi.ama-assn.org/cgi/content/full/161/3/282>.

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**Brian Strom, MD, MPH**, Director of the CCEB, Associate Vice Dean, University of Pennsylvania SOM, was interviewed about his study on soy formula (which found no differences between those fed soy- vs. milk-based formulas as infants) in the column “Carnal Knowledge: Take that talk about soy with a grain or two of salt,” which appeared on January 1<sup>st</sup> in *The Philadelphia Inquirer* (<http://www.philly.com/mld/philly/entertainment/16359614.htm>). Dr. Strom’s study can be read at: <http://jama.ama-assn.org/cgi/content/full/286/19/2402>.

Dr. Strom was also quoted, along with Scott Halpern, MD, PhD, MBE, MSCE, a fellow in the Division of Pulmonary, Allergy and Critical Care Medicine and senior fellow with the Center for Bioethics, and **Ross Koppel, PhD**, Adjunct Professor of Sociology in the Penn School of Arts and Sciences and an affiliate member of the CCEB, in an article that first appeared in the Saturday, January 13, 2007 edition of *CIO Unified Communications: Australia’s Magazine for Information Executives*. The article, entitled “Right Tech Dose Helps Medicine Go Down,” can be read here: <http://www.cio.com.au/index.php/id:1249455314;fp:16;fpid:0>.

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**Yu-Xiao Yang, MD, MSCE**, Assistant Professor of Medicine and Epidemiology, Gastroenterology Division, University of Pennsylvania SOM, Senior Scholar in the CCEB, was quoted in *Associated Press* and

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Reuters articles that were picked up in numerous newspapers, including *The New York Times* and *The Boston Globe*, as well as by national and local TV news reports about his study reporting that people over 50 who took popular heartburn drugs for a year or more had a significant increase in the risk of breaking a hip. The study, co-authored by **James Lewis, MD, MSCE**, Associate Professor of Medicine, Gastroenterology Division, Senior Scholar in the CCEB, Solomon Epstein, MD, Division of Gastroenterology Penn SOM, and David C. Metz, MD, Division of Endocrinology, Penn SOM, was published in the December 27<sup>th</sup> issue of *JAMA* (<http://jama.ama-assn.org/cgi/content/full/296/24/2947>).

### Notes

**Shiriki Kumanyika, PhD, MPH**, Associate Dean for Health Promotion and Disease Prevention, University of Pennsylvania SOM, Director, Graduate Program in Public Health Studies, University of Pennsylvania, Professor of Epidemiology, University of Pennsylvania SOM, and Senior Scholar in the CCEB, was one of three award winners to receive the *Woman's Day* Red Dress Award on February 1<sup>st</sup> in New York City in recognition of her work in the fight against heart disease in women. Dr. Sharon Hayes, from the Mayo Clinic, and Dr. Susan Bennett, from Georgetown Hospital, were the other recipients. This award, given annually since 2004, is based



**Dr. Kumanyika accepting the Woman's Day Red Dress Award**

on nominations from the National Heart Lung and Blood Institute (NHLBI), the American Heart Association, and former honorees.

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**Hedi Schelleman, PhD**, a postdoc in the Epidemiology Department, Center for Clinical Epidemiology and Biostatistics, won the Roger R. Williams Award for Genetic Epidemiology and the Prevention and Treatment of Atherosclerosis presented at the 47th

Annual Conference on Cardiovascular Disease Epidemiology and Prevention. She presented her abstract on Saturday, March 3rd in Orlando, FL as part of the special Third-Day Program entitled Translational Genomics: How To Design and Analyze Genome-Wide Association Studies for Cardiovascular Diseases. Dr. Schelleman's abstract was the one to achieve the highest average score among abstracts submitted in the genetic epidemiology category.

The Roger R. Williams Memorial Award for Genetic Epidemiology and the Prevention and Treatment of Atherosclerosis is named for Dr. Roger R. Williams' pioneering work in genetics of inherited lipid disorders and the prevention of atherosclerosis.

(Bellamy, continued from page 4)

she is PI of an R13 grant currently funded by the National Institute of General Medicine Sciences (NIGMS) entitled "Fostering Diversity in Biostatistics" for ENAR. In this role, Dr. Bellamy has organized or co-organized a half-day workshop by the same name every year at the annual ENAR conference since completing her graduate degree in 2001. The last workshop was held on March 11, 2007 in Atlanta, GA and attracted nearly 70 pre-registrants, including current graduate, undergraduate and high school students, from races/ethnicities traditionally under-represented in Biostatistics and Public Health.

Dr. Bellamy has been the lead or contributing author of articles that have been published in various journals, including: *AIDS*, *American Journal of Respiratory and Critical Care Medicine*, *Archives of Internal Medicine*, *Cancer Epidemiology, Biomarkers & Prevention*, *Clinical Trials*, *Contemporary Clinical Trials*, *Contraception*, *Fertility and Sterility*, *Hepatology*, *Innovations in Family Medicine Education*, *Journal of Clinical Epidemiology*, *Journal of Computational and Graphical Statistics*, *Journal of Foot and Ankle Surgery*, *Journal of Health Communication*, *Journal of Transplantation*, *Medicine and Science in Sports and Exercise*, *Statistica Sinica*, *Statistical Methods in Medical Research*, and *Statistics in Medicine*.

Dr. Bellamy lives in the Mt. Airy section of Philadelphia with her partner where they try to stay active and connected with friends in the area. Dr. Bellamy is also an avid restaurant goer, and ran her first half marathon in September.

or Darwinistic, paradigm. His doctoral dissertation, "Evolution-Assisted Discovery of Sentinel Features in Epidemiologic Surveillance," was the first effort to adapt and apply evolutionary computation methods called "learning classifier systems" to biomedical data mining. He has published and presented extensively in national and international venues on using evolutionary computation in biomedical KDD.

Dr. Holmes is particularly interested in injury research. He has worked with Drs. Dennis Durbin, a CCEB Senior Scholar, and Flaura Winston on Partners for Child Passenger Safety, a project sponsored by the State Farm Insurance Company, and a project currently funded by the Center for Child Injury Prevention Science to investigate causes of death in children killed in motor vehicle crashes. Dr. Holmes is also extending his work in KDD to the bioinformatics domain, where he is working with a team led by Dr. Harold Feldman to investigate patterns of amino acids in the HLA molecule that may be associated with renal allograft rejection.

Dr. Holmes's research also involves creating computerized interventions that are designed to encourage health communication and shared decision-making between patients and physicians. This field, while well-known in the health communication and psychology domains, is relatively new to medical informatics. Dr. Holmes has worked on several such projects, including Heart Sense, an interactive, game-based, computerized intervention to reduce delay in seeking care for acute coronary syndrome, developed under the leadership of Dr. Barry Silverman in Penn's School of Engineering and Applied Science and in collaboration with Drs. Stephen Kimmel and William Holmes in the CCEB. Currently, Dr. Holmes is Principal Investigator of a project looking at physician and patient factors involved in discussing prostate cancer screening, with the goal of designing a computerized intervention to provide men with the skills needed to engage in this discussion with their physicians. This study is one of four interrelated projects within the Penn Center for Population Health and Health Disparities, led by Dr. Timothy Rebbeck, that looks to bring knowledge about biological, behavioral, social environmental and physical environmental factors that create health disparities in men at risk of or diagnosed with prostate cancer. Dr. Holmes is also working on a

game-based computer intervention to teach children about the proper use of antibiotics in common respiratory infections. An article on which he collaborated titled "Computer games may be good for your health" was published in the Journal of Healthcare Information Management, and he has presented or co-authored numerous abstracts on this topic at national meetings.

In addition to his research, Dr. Holmes has a busy teaching schedule in the CCEB's masters', doctoral, and certificate programs. He is a course director and instructor for Database Management for Clinical Epidemiology, Introduction to Medical Informatics, Introduction to Epidemiologic Research Methods, Practical Applications in Clinical Research Methods, and Database Management here at Penn. Dr. Holmes is also very active in the American Medical Informatics Association, where he serves as the Chair of the Education Committee and member of a number of steering committees, and is co-leading a national effort to establish essential competencies in medical informatics. He was the founding Chair of AMIA's Knowledge Discovery and Data Mining Working Group. His contributions to the field of medical informatics were recognized formally this past November, when he was inducted as a Fellow in the American College of Medical Informatics.

Dr. Holmes is also active outside the informatics world, serving as Chair of the Evaluation Working Group for the Centers for Population Health and Health Disparities, a national group consisting of eight NIH-funded centers including the University of Pennsylvania.

Dr. Holmes resides in University City with his wife Jennifer, and daughters Hazel and Monika. They are (slowly) restoring their 100-year-old house, which gives John plenty of opportunity to engage in a favorite hobby, woodworking. That is, when he's not busy cooking, which he does a lot. John is also an avid bicyclist and enjoys exploring the many miles of trails and paths in Fairmount Park and beyond. He is looking forward to training for the MS150 and several other long-distance rides this year.

### Time sequence

The drop in breast cancer incidence followed a drop in use of HRT, but, as noted above, perhaps too quickly to be a result of declines in hormone use. As noted in the JNCI article cited above, in the state of Minnesota breast cancer incidence rates began to decline in 2000, before the results of the WHI were published, and continued through 2003, but seemed to be leveling off in 2004.

### Study Design

This is a weak study design. Ecological data comparing secular trends in breast cancer incidence and in use of hormone therapy can only be suggestive, because the joint distribution of breast cancer incidence and hormone use at the individual level is unknown. Uncontrolled confounding is also a potential problem. Studies have found that women on hormone therapy are more likely to get mammograms than those who are not taking hormones. If the women who stopped using hormones also started to have mammograms less consistently, breast cancer incidence could drop in the short run because early cancers are not being found. It is not clear if mammography rates have declined. The McNeil article reports that there were drops between 2000 and 2003, with the largest decline, 3.2%, in women ages 50-69. National surveys do not show a decline in mammography utilization among women ages 40 and older in recent years but again these reflect secular trends and not individual-level data. In 2000, 71% of white women and 68% of black women reported a mammogram; in 2003, 70% of each group did so (<http://www.cdc.gov/cancer/breast/statistics/screening.htm>).

Stronger designs would include case-control studies such as the Women's CARE study described above, or cohort studies comparing breast cancer incidence in women who continued taking hormones with those who quit. The WHI is following study subjects initially randomized to the hormone or the placebo arms of the study to see whether or when increased risk associated with estrogen use declined once women stopped taking the drug.

**SE:** Indeed, the observation is provocative but *not* definitive. Data from 2004 from SEER will be available in April; it will be of great interest to see whether the decline persists.

**Q:** *Is such a large drop in cancer rates in such a short time really plausible?*

**SE:** The drop is certainly dramatic, but the study authors make a good case that these results are not implausible. They did not project that cancers were actually declining, but rather that women who had as-yet undetectable breast cancer who had been taking hormone therapy (which would have been promoting tumor growth) and then stopped, might have experienced a major slowing in growth of their tumors such that tumors that might otherwise have been detected remained under the detection threshold. The fact that the decrease was most evident for ER+ tumors was consistent with this hypothesis.

**Q:** *What should women do to alleviate menopausal symptoms?*

**SN:** Women suffering from menopausal symptoms are particularly vulnerable to claims of relief to be obtained with this or that compound. News reports are often overstated and contradictory.

I would suggest that women seek up-to-date information from reliable sources and make their own decisions after consulting their doctor. One informative site is the WHI website ([http://www.nhlbi.nih.gov/health/women/pht\\_facts.pdf](http://www.nhlbi.nih.gov/health/women/pht_facts.pdf)), which provides a clear overview of the design and findings of that study, along with their recommendations for non-hormonal approaches to menopausal symptoms. Another is the website of the National Women's Health Information Center of the US Department of Health and Human Services (DHHS): [www.4women.gov](http://www.4women.gov). This site provides summaries of recent studies, such as a randomized study comparing complementary/alternative medicines and hormone replacement therapy for relief of



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menopausal symptoms, which was reported in the *Annals of Internal Medicine* in December 2006. The authors found that only HRT (estrogen alone or estrogen + progesterone) was effective in reducing the number of menopausal symptoms.

The bottom line is that a woman's decision will involve balancing risks and benefits of different approaches. Starting with simple, safe approaches such as avoiding hot or spicy foods or alcohol if they trigger hot flashes, drinking ice water, layering clothes, and sleeping in cool rooms makes sense. If no approaches short of HRT work, then women are advised to take the lowest possible dose for the shortest possible time.

**Q:** *What do postmenopausal women need to know about HRT?*

**SE:** They certainly need to know that, rather than providing cardiovascular benefit as was promoted for many years based on epidemiological data, HRT use actually increases risk for cardiovascular outcomes. (A somewhat earlier study, the Heart and Estrogen/Progestin Replacement Study (HERS), documented increased risk for HRT users who already suffered from cardiovascular disease.) For those women who have intolerable menopausal symptoms and for whom no alternative therapy is sufficiently effective, HRT may be a reasonable option but should be used for as short a duration as possible. Women who are considering initiating HRT, or who are current users and are considering whether to stay on or discontinue, should be having serious discussions with their physicians about the risks and benefits.

**Q:** *Can you describe the Women's Health Initiative—what was it studying and what did it find?*

**SN:** The WHI was a very large multi-faceted study that evaluated the effects of hormone replacement therapy, calcium, and diet on a number of health outcomes. One of the main questions was whether hormone replacement therapy could have beneficial effects on cardiovascular outcomes, osteoporosis, and cognitive decline, without incurring harmful effects such as increased incidence of breast cancer. Prior

observational studies had suggested beneficial effects for cardiovascular disease, osteoporosis and Alzheimer's disease with HRT, and other observational studies had found an increased risk of breast cancer with combined estrogen/progestin HRT, with mixed results for estrogen alone. The WHI study was designed to be large enough to find beneficial effects if any and to detect small increases in adverse outcomes. The randomized component of the study included two groups of women defined by whether or not they still had an intact uterus. Women who had had a hysterectomy and no longer had a uterus were not at risk of uterine cancer resulting from estrogen given alone. 10,000 women were assigned to estrogen alone or to placebo.

Among women who still had an intact uterus, over 16,000 women were assigned to either estrogen + progestin or placebo. Because its goal was to study the benefit of HRT on various chronic disease outcomes affecting older women, the mean age of women recruited into the HRT studies was 64 and all were postmenopausal. Interestingly, at the time of randomization, very few of the women were taking HRT, 13% in the estrogen group and 6% in the E+P group, even though close to three times that many had ever used HRT in the past, suggesting that these women may have ceased to experience menopausal symptoms. Many have argued that the results of the study are not relevant to women who have not yet reached menopause and who are likely experiencing the greatest number of menopausal symptoms.

The E+P arm of the study was terminated after 5.2 years of follow-up because of a greater than expected increase in breast cancer incidence, as well as incidence of heart attacks, strokes and blood clots in the legs.

**Q:** *What are the actual implications of the WHI?*

**SE:** The WHI was designed and conducted to evaluate the risks and benefits of long-term use of hormone replacement therapy. Observational data had suggested that HRT might reduce risk of cardiovascular disease in addition to alleviating menopausal symptoms. It was expected that HRT would reduce fracture risk based on its documented increase in bone mineral density. On the negative side,

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## CCEB's Clinical Research Services: BAC, BECC, and CRCU Service Centers

*The CCEB serves as an interdisciplinary resource for clinical research throughout the School of Medicine. It offers a range of services and training programs, primarily for faculty, residents, and fellows within the University of Pennsylvania Health System, but also for clinicians and scientists in other schools at Penn and throughout the Delaware Valley. These programs and services are identified and described as a regular feature of this newsletter.*

The clinical research services provided by CCEB faculty and staff include biostatistical support provided by the Biostatistics Analysis Center (BAC); study design and biostatistical consultation and advice provided by the Biostatistics and Epidemiology Consulting Center (BECC); and project management, data management, and research technology services provided by the Clinical Research Computing Unit (CRCU). Each operates as a service center and is directed by faculty leaders within the CCEB.

The BAC provides professional MS- and PhD-level biostatistical support, specializing in: statistical programming and analysis using various commercially-certified statistical software packages such as SAS, S-Plus, STATA, StatXact and SUDAAN for data analysis support; statistical data management support of analytic activities at any stage of a research project, specifically the preparation of analysis files for statistical software packages; and technical report preparation, including the summarization of results and interpretations of statistical analysis of research data. Thomas Ten Have, PhD, MPH, is the Faculty Director for the BAC; John Farrar, MD, PhD, is the Associate Faculty Director. Amy Praestgaard, MS, is the Managing Director and Senior Biostatistician and provides day-to-day operational direction for the BAC. Those interested in additional information about the BAC, including details about support services and the fee structure for these services should review the website (<http://www.cceb.med.upenn.edu/services/bac/>). An online request form should be submitted to request services provided by the BAC (<http://www.cceb.upenn.edu/pages/apps/ProjectCollab/registerContact.html>). Ms. Praestgaard should be contacted directly for additional questions (215-573-4859, [praestga@mail.med.upenn.edu](mailto:praestga@mail.med.upenn.edu)).

The BECC is the portal for many of the services offered by the CCEB to the Penn community. CCEB faculty and staff, through the BECC, offer free short-term data analysis/study planning assistance subsidized by the CCEB. Types of assistance include design, epidemiologic, and analysis strategies for re-

search proposals, including sample size calculations for observational, experimental, and survey research studies; data analysis; and outcome measurement methodology consulting on a limited basis for qualifying faculty and fellows who do not have access to financial resources. Long-term collaborations with CCEB faculty are encouraged. Thomas Ten Have, PhD, MPH, is the Faculty Director for the BECC; John Farrar, MD, PhD, is the Associate Faculty Director. Amy Praestgaard, MS, is the Managing Director and generally is the first contact for investigators submitting requests. Those interested in additional information about the BECC should review the website (<http://www.cceb.med.upenn.edu/services/becc/>). An online request form should be submitted to request services provided by the BECC (<http://www.cceb.upenn.edu/pages/apps/ProjectCollab/registerContact.html>). Ms. Praestgaard should be contacted directly for additional questions (215-573-4859, [praestga@mail.med.upenn.edu](mailto:praestga@mail.med.upenn.edu)).

The CRCU provides clinical data management and research computing support for a wide range of clinical research projects throughout the SOM. The CRCU is staffed with project management, clinical data management, and research computing professionals who support the development and implementation of large-scale, multicenter clinical trials, collaborative clinical and patient-oriented research, and multi-institutional health services research projects for researchers within Penn and other academic institutions. The development and support activities of the CRCU involve application development, database administration, project management, clinical data management, research computing, and technology support services. Harold I. Feldman, MD, MSCE, and J. Richard Landis, PhD, are the Faculty Co-Directors. Those interested in additional information about the array of technical and non-technical services provided by the CRCU, as well as information about the rates and fee structure for these services, should review the website (<http://www.cceb.med.upenn.edu/services/crcu/>). An online request form should be submitted to request

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services provided by the CRCU (<http://www.cceb.upenn.edu/pages/apps/ProjectCollab/registerContact.html>). Questions should be directed to Conley Heaberlin (215-573-4789) or Florence Speiser (215-573-5765) or via email ([propdev@mail.med.upenn.edu](mailto:propdev@mail.med.upenn.edu)).

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there was concern that it could fuel the rate of breast cancer. All of these major risks and benefits were carefully monitored for as the study progressed. The study was terminated early because the hoped-for cardiovascular benefits not only did not pan out, the risks increased in those on HRT compared to those on placebo. The data on fracture and breast cancer were consistent with the prior expectations. So the implications were that overall, women should not be taking HRT for the long-term to improve their fundamental health; from a public health perspective, the risks relative to cardiovascular disease and breast cancer would appear to outweigh the benefits in preventing osteoporotic fractures.

**Q:** *What additional studies are needed to corroborate the reported findings?*

**SE:** You would need to look at changes in breast cancer incidence as well as changes in use of hormones. If the rates of HRT use were lower in other countries than in the US, however, you would not expect such a dramatic decline in breast cancer incidence that could possibly be attributable to women discontinuing use of HRT. Certainly, additional follow-up of the observational data in the US is needed. If the hypothesis that the drop seen in 2003 is in fact attributable to the slowing of growth of existing tumors, we might see an increased incidence in the future.

## 2007 Clinical Research Certificate Recipients

*Congratulations and best wishes to those who have been awarded Clinical Research Certificates!*

### April 2007

Sigrid E. Berg, MD, MPH

Nissa Christine Blocher, MD

Meredith Lee Heltzer, MD

Wilfried Mai, DVM, PhD

Manoj K. Mittal, MD

Suresh G. Shelat, MD, PhD