Breast cancer incidence in Marin County: a hotspot grows cold

Christina A. Clarke, PhD
Greater Bay Area Cancer Registry

NAACCR
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Objectives

Elevated incidence of breast cancer in Marin County in late 1990’s/early 2000’s

• Review history of public concern
• Summarize scientific publications

Changing incidence of breast cancer in Marin County and elsewhere in 2003

• Summarize changes and associated literature

Most recent breast cancer incidence in Marin through 2012

• Summarize recent (2015) report and its conclusions

Women’s Health Initiative follow-up for breast cancer after quitting EP

• Discuss relevance to breast cancer incidence patterns in Marin County
History: Marin County as a breast cancer hotspot

1994: report of elevated rates of invasive breast cancer in non-Hispanic white women in the Bay Area
History: Marin County as breast cancer hotspot

1995-96: County health department and advocacy groups become involved
1998: Rates same as similar sub-county regions

Evaluating local differences in breast cancer incidence rates: A census-based methodology (United States)

Angela Witt Prehn and Dee W. West

*Cancer Causes and Control, 1998, 9, pp. 511-517*

Table 2. Age-adjusted incidence rates of breast cancer by block-group risk factor for Marin County, block-groups with risk factors like Marin County (high-risk), and block-groups with risk factors not like Marin County (low-risk)

<table>
<thead>
<tr>
<th>Risk factor (cutoff for high risk)</th>
<th>Marin County (reference)</th>
<th>High-Risk block-groups</th>
<th>Low-Risk block-groups</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Rate</td>
<td>N</td>
</tr>
<tr>
<td>Parity (&lt;1.33 children/woman)</td>
<td>169</td>
<td>119.3</td>
<td>1216</td>
</tr>
<tr>
<td>Urban/rural residence (urban)</td>
<td></td>
<td></td>
<td>6729</td>
</tr>
<tr>
<td>Household income (&gt;50 000)</td>
<td></td>
<td></td>
<td>1683</td>
</tr>
<tr>
<td>Poverty level (≤5%)</td>
<td></td>
<td></td>
<td>2935</td>
</tr>
<tr>
<td>College education (&gt;45%)</td>
<td></td>
<td></td>
<td>1104</td>
</tr>
<tr>
<td>Working class occupation (&gt;50%)</td>
<td></td>
<td></td>
<td>1664</td>
</tr>
</tbody>
</table>

a Statistically significantly different than high-risk block-groups at p < 0.05.

b Total number of block-groups differs by risk factor due to missing values.

The table shows that for each risk factor, block-groups with characteristics similar to those in Marin County had a statistically significantly higher breast cancer incidence rate than block-groups that were not like Marin County with regards to these characteristics.
3.6% increase/year (95% CI, 1.8-5.5)
6x more rapid than in comparison areas
Mortality: stable, hint of continued decrease
Ages 45-64 at diagnosis identified as group with excess incidence

Marin had same prevalence of HT, mammography as other regions
Excess breast cancers mostly for ER+/PR+ tumors occurring in women aged 50-69
Breast cancer amid affluence / High rate in Marin County appears tied to wealth, education

Ulysses Torassa, Chronicle Health Writer   Published 4:00 am, Sunday, January 26, 2003

Breast cancer incidence in Marin County

White, non-Hispanic women, invasive cancers only.
Age-adjusted rate per 100,000

Source: Northern California Cancer Center

Chronicle Graphic
Breast cancer incidence increase in Marin County: summary

Consistent increase in rates of invasive breast cancer
Specific to first primary tumors
Mostly observed for:
   - Ages 50-69 at diagnosis
   - Hormone-sensitive tumors
   - Early stage
Stable mortality rates
Rates comparable to other sociodemographically similar populations
Message: “It’s the demography, not the geography”
Annual incidence rates of breast cancer in non-Hispanic white women 1988-2012

2001-03 decline: 27%
Recent Declines in Hormone Therapy Utilization and Breast Cancer Incidence: Clinical and Population-Based Evidence

Christina A. Clarke and Sally L. Glaser
Surveillance Research, Northern California Cancer Center, Fremont CA, and Department of Health Research and Policy, Stanford University School of Medicine, Stanford, CA
Connie S. Uratsu, Joseph V. Selby, Larry H. Kushi, and Lisa J. Herrinton
Division of Research, Kaiser Permanente, Oakland CA

- First publication describing rate change and relating it to HT use
- Incidence tracks to in HT changes after WHI trial data release in 2002

Clarke et al., J Clin Oncol, 2006
The Decrease in Breast-Cancer Incidence in 2003 in the United States

Peter M. Ravdin, Ph.D., M.D., Kathleen A. Cronin, Ph.D., Nadia Howlader, M.S., Christine D. Berg, M.D., Rowan T. Chlebowski, M.D., Ph.D., Eric J. Feuer, Ph.D., Brenda K. Edwards, Ph.D., and Donald A. Berry, Ph.D.

2001-2004 changes SEER

Overall: -9%
Ages 0-49: +1%
Ages 70+: -11%
Ages 50-69: -12%
ER+: -15%
ER-: -2%
No difference by stage
Limited to first primary tumors
Decline in breast cancer incidence after decrease in utilisation of hormone replacement therapy

Schleswig-Holstein, Germany

2001-2004 changes

Overall: -5%

Ages 0-49: +1%

Ages 70+: -11%

Ages 50-69: -12%

ER+: -15%

ER-: -2%

No difference by stage

Limited to first primary tumors
California: regional differences in EP use tracked closely to breast cancer declines

<table>
<thead>
<tr>
<th>County Group by Prevalence of EP Use in 2001</th>
<th>Prevalence of EP Use per 100,000 Women</th>
<th>Age-Adjusted Incidence of Invasive Breast Cancer per 100,000 Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2001</td>
<td>2003</td>
</tr>
<tr>
<td>Low*</td>
<td>16,400</td>
<td>5,300</td>
</tr>
<tr>
<td>Medium†</td>
<td>22,800</td>
<td>6,100</td>
</tr>
<tr>
<td>High‡</td>
<td>25,800</td>
<td>6,800</td>
</tr>
</tbody>
</table>

Data limited to non-Hispanic white women aged 45-74 at diagnosis
* Includes the counties of Butte, El Dorado, Kern, Kings, Madera, Mendocino/Lake, Placer, Riverside, San Joaquin, San Mateo, Siskiyou/Lassen/Modoc/Trinity, Stanislaus, Sutter/Yuba, and Tehama/Colusa/Glenn.
† Includes the counties of Fresno, Humboldt/Del Norte, Imperial, Los Angeles, Merced, Monterey/San Benito, Nevada/Plumas/Sierra, Orange, Sacramento, San Bernardino, San Diego, San Luis Obispo, Santa Barbara, Santa Clara, Shasta, Solano, Sonoma, Tulare, and Tuolumne/Alpine/Amador/Calaveras/Inyo/Mariposa/Mono
‡ Includes the counties of Alameda, Contra Costa, Marin, Napa, San Francisco, and Santa Cruz.

Robbins and Clarke, JCO 2007
Breast cancer incidence changes in 2003: summary

Sudden, unprecedented decline in invasive cancer in 2003 reported in California, SEER, Germany, New Zealand

Specific to first primary tumors, mostly ages 50-69

More marked for:

- Hormone-positive tumors
- Small/early stage than large/late stage tumors

*In situ:* decline in California, not in SEER

Mortality: continued declines

Ecologic correlation of declines with higher prevalence of EP use
• Funded by federal earmark to Marin DHHS in 2005

• All women seeking mammograms in county late 2006-2010 asked to contribute detailed questionnaire and saliva sample

• Over 13,000 participants

• Many UCSF investigators on steering committee

• Singular resource for detailed HT use information
Recent trends in hormone therapy utilization and breast cancer incidence rates in the high incidence population of Marin County, California

Rochelle R Eremann, Lee Ann Prebil, Mary Mockus, Kathy Koblick, Fern Orenstein, Christopher Benz and Christina A Clarke

Prevalence of EP use in Marin found to be high due to low proportion of women with hysterectomies.
Recent trends in breast cancer incidence and mortality in Marin County, California, 1988-2012

An Update from the Greater Bay Area Cancer Registry
September 21, 2015

Christina A. Clarke, Ph.D., Meg McKinley, M.P.H., Sally L. Glaser, Ph.D.
Cancer Prevention Institute of California and Stanford Cancer Institute
Correspondence: tina@cpic.org

Executive summary:
As part of our regular surveillance of cancer in the nine-county Greater Bay Area region of California, the Greater Bay Area Cancer Registry has carefully assessed recent trends in breast cancer incidence in the non-Hispanic white female population of Marin County, a population for whom elevated rates had been reported in the past. Our review of the most complete incidence data (1988-2012) and mortality data (1988-2013) available, finds:

The hotspot cools off

- **Incidence**
  - 2012 rate—130 cases per 100,000 women—lowest reported since 1988
  - 31% decline from the peak rate in 2001

- **Mortality**
  - 2013 rate—16 deaths per 100,000 women—lowest reported since 1988
  - 65% decline from rate in 1988

- **Comparison to other regions**
  - Similar trends to those in Bay Area, California
  - No evidence of a geographic excess in Marin since mid-2000’s
Annual incidence rates of breast cancer in non-Hispanic white women 1988-2012
Annual mortality rates of breast cancer in non-Hispanic white women 1988-2013
Why? Mammography?

- 2009 recommendations for population-wide screening revised; biennial screening 50-74 only
- Screening adherence data: stable trends thru 2013
- *In situ* breast cancer incidence
  - Should be 1st indication of reduction in mammography
  - Did not decline, rather increased significantly
- Incidence in women aged outside recommended ages
  - No age variation in patterns
- Comparison to other regions
  - Similar trends to Bay Area, California
- Expert opinion: no obvious influence of mammographic screening change
Annual incidence rates of breast cancer in Marin County by stage 1988-2012*

*Non-Hispanic white women only
Why? Other reasons?

- Prevalence of menopausal hormone therapy (HT) use measured as high in Marin County women as part of Marin Women’s Study
  - More women used estrogen/progestin combined HT than elsewhere
  - Sharp reduction in HT use reported in Marin and elsewhere in 2003
  - Hormone sensitive breast cancers among women aged 50-69 fell notably in 2003-3004
- Marin Women’s Study: HT quitters did not reinitiate use, and newly menopausal women never initiated use
- Expert opinion: excess rates of late 1990’s consistent with HT use
Getting message to the public

Marin County no longer a hot spot for breast cancer, study finds
By Victoria Colliver  Updated 12:31 pm, Wednesday, October 7, 2015

Marin County’s Breast Cancer Rate Has Plummeted. Why?

Marin County Breast Cancer Rate
SINCE 2001

31%
Source: Cancer Prevention Institute of California

TINA CLARKE
CANCER PREVENTION INSTITUTE OF CALIFORNIA
Peer-reviewed publications


Long-term effects of EP on breast cancer?

Breast Cancer After Use of Estrogen Plus Progestin and Estrogen Alone
Analyses of Data From 2 Women’s Health Initiative Randomized Clinical Trials

Rowan T. Chlebowski, MD, PhD; Thomas E. Rohan, PhD; JoAnn E. Manson, MD, DrPH; Aaron K. Aragaki, MS; Andrew Kaunitz, MD; Marcia L. Stefanick, PhD; Michael S. Simon, MD; Karen C. Johnson, MD, MPH; Jean Wactawski-Wende, PhD; Mary J. O’Sullivan, MD; Lucile L. Adams-Campbell, PhD; Rami Nassir, PhD; Lawrence S. Lessin, MD; Ross L. Prentice, PhD
Overall hazard ratio (HR) and 95% CI (black line and gray-shaded region, respectively) are shown for the effect of conjugated equine estrogens plus medroxyprogesterone acetate (CEE + MPA) on the risk of invasive breast cancer compared with placebo during the intervention period (left panel) and the overall postintervention phase (right panel). A reference line (dotted black) at unity corresponds to no differential risk between randomization groups. Dashmarks (bottom of right panel) indicate the early and late postintervention periods. Time-varying linear HR and 95% CI (orange lines) are also displayed for the intervention period (left panel) and overall postintervention period (right panel), as well as a time-varying linear HR for the early postintervention phase (hashed orange line). Biennial HRs and 95% CIs (solid blue lines and blue-shaded regions, respectively) are presented as an alternate description for time-varying risk. The biennial HR (95% CI) were 0.71 (0.47-1.08), 1.36 (0.95-1.94), 1.65 (1.17-2.32) during the intervention, and 1.29 (0.88-1.88), 1.18 (0.80-1.74), 1.36 (0.91-2.02), and 1.49 (0.96-2.33) for the postintervention phase. Significance tests of the time-varying linear HR for the primary (adherence adjusted) analysis were conducted and yielded \( P = .008 (.007) \) for linear trend during the intervention; \( P = .28 (.04) \) for linear trend during the early postintervention phase; \( P = .07 (.006) \) for difference between linear trends of intervention and early postintervention phase; \( P = .86 (.65) \) for linear trend during the overall postintervention phase; and \( P = .04 (.02) \) for difference between linear trends of intervention and overall postintervention phase. Time-varying linear HRs were not shown for the late postintervention phase because significance tests were not suggestive of a trend: \( P = .96 (.55) \) for a linear trend during the late postintervention phase.

- a HR, 1.24 (95% CI, 1.01-1.53).
- b HR, 1.32 (95% CI, 1.08-1.61).
- c HR, 1.23 (95% CI, 0.90-1.70).
- d HR, 1.37 (95% CI, 1.06-1.77).
The human breast is a well-organized ductal network ending in terminal ductal lobular units, which are hormone sensitive. The mammary epithelium is home to a heterogeneous populations of cells that contain basal and myoepithelial cells, stem cells, luminal differentiated cells, and luminal progenitors, some of which contain hormone receptors (PR). Progesterone is thought to act through PR-positive (PR+) luminal cells and activate PR-negative (PR-) cells via paracrine signals, such as receptor activator of nuclear factor-κB ligand (RANKL) and wingless-int (WNT), expanding the number of stem/progenitor cells to generate a more complex and denser epithelium. Estrogen + progesterone (E + P) exposure during hormone therapy is likely to harness these cellular and mitogenic mechanisms, thus increasing breast cancer risk. New data from the Women's Health Initiative clinical trials have provided further insight into the early and late postintervention effects of progesterone exposure on breast cancer risk. Plausible underlying biological mechanisms for these time-varying risk alterations are illustrated.

Joshi et al, JAMA Oncol 2015
CANCER PREVENTION INSTITUTE OF CALIFORNIA

Preventing Cancer. Promoting Life.