Applying current knowledge to accelerate cancer prevention: what is preventable and how?

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Graham A Colditz, MD DrPH
Niess-Gain Professor
Department of Surgery
Division of Public Health Sciences
Conflict of interest

- I have no financial relationships to disclose

- I will not discuss off-label use and or investigational use in my presentation
Why are we not preventing cancer now?

Multiple barriers:
- Skepticism that cancer can be prevented
- Short term focus of cancer research
- Interventions deployed too late in life
- Research focused on treatment not prevention
- Debates among scientists
- Societal factors ignored
- Lack of transdisciplinary training
- Complexity of implementation

Colditz et al Sci Transl Med 2012: March 28
Why are we not preventing breast cancer now?

Multiple barriers:

• Skepticism that cancer can be prevented
• Time frame: Short term focus of research
• Time frame: Interventions too late in life
• Research focused on treatment not prevention
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• Societal factors ignored
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Colditz et al Sci Transl Med 2012: March 28
Overcoming obstacles of skepticism and time frame

• Must counter skepticism that cancer can be prevented
  ▪ Goals of prevention: risk marker, premalignant lesion, invasive disease, death
  ▪ Avoid exposure vs. remove later in life
  ▪ Can we intervene if we don’t have the pathway defined?

• Take into account time frame of cancer development
Evidence that cancer is preventable

- Migrant studies
  - No US lifestyle
- Within country changes
  - Remove HRT, Korea rapid increase, etc
- Randomized Controlled Trials of SERMs,
  - Tamoxifen, Raloxifene
- Bilateral oophorectomy for women with BRCA1/BRCA2
Fig. 1. Trend toward earlier menarche in some European countries. (Sweden (□—□); Norway (■—■); Finland (●—●); Denmark (△—△); Holland (○—○); United Kingdom (▲—▲); United States (∗). (From Tanner, 1978.)
Change in menarche, Korea

30 years

Cho Eur J Pediatr 2009
Breast Cancer Incidence, Korea

1998 40, born 1958
2008 40, born 1968

Jung et al, J Breast Ca, 2011
RCT: Rates breast cancer P1 trial
Tamoxifen vs. placebo

Fisher et al, 1998; 90:1371-88
Evidence that breast cancer is preventable

- Migrant studies
  - No US lifestyle
- Within country changes
  - Remove HRT, Korea rapid increase, etc
- RCTs of SERMs,
  - Tamoxifen, Raloxifene
- Bilateral oophorectomy for women with BRCA1/BRCA2
  - 10 studies, HR 0.49 (0.35, 0.64)
  - Rebbeck JNCI 2009;101:80-7
### Summary of breast cancer prevention strategies

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Risk group</th>
<th>% US pop</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bilateral oophorect-y</td>
<td>BRCA1/2</td>
<td>&lt;1%</td>
<td>50% ↓</td>
</tr>
<tr>
<td>Tamoxifen / Raloxifene</td>
<td>&gt;1.67% 5-yr risk</td>
<td>10-40%</td>
<td>50% ↓</td>
</tr>
<tr>
<td>Weight loss (22lb)</td>
<td>Overweight + obese</td>
<td>60%</td>
<td>50%*</td>
</tr>
<tr>
<td>Increase exercise</td>
<td>&lt;30 min/d</td>
<td>&gt;60%</td>
<td>Timing matters</td>
</tr>
</tbody>
</table>

* Loss after menopause based on Eliassen JAMA, 2006
What is preventable?

• More than 50% of all cancer can be prevented with what we know now
• How big is the reduction due to lifestyle?
• How long will we wait?
How do we know lifestyle is important?

- International variation in rates of cancer
  - Diet, physical activity, obesity, and environmental exposures
- Migrant studies
  - Account for genetic predisposition
  - Japanese who migrated to Hawaii and CA
  - Italians and Greeks who migrated to Australia
- Trials and other studies
  - Vaccines
  - Anti-estrogens (Tamoxifen & Evista)
Proportion of cancer deaths attributed to non-genetic factors.

## Lifestyle: high income countries

<table>
<thead>
<tr>
<th>Cause</th>
<th>% cancer caused</th>
<th>Magnitude possible reduction</th>
<th>Time (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>33</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overweight/obesity</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diet</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of exercise</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viruses</td>
<td>5-7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Family history</td>
<td>5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UV/ionizing radiation</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reproductive</td>
<td>3</td>
<td></td>
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Tobacco control: population wide strategies

MPOWER

- **M**onitor tobacco use and prevention policies
- **P**rotect people from tobacco smoke
- **O**ffer help to quit tobacco use
- **W**arn about the dangers of tobacco
- **E**nforce bans on tobacco advertising, promotion, and sponsorship
- **R**aise taxes on tobacco

Implement Framework Convention on Tobacco Control
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<td>0</td>
<td>N/A</td>
</tr>
</tbody>
</table>
Time course: lung & total mortality

Current smoker: continuing
Infections

- Helicobacter pylori
- HPV
- Hepatitis B
- Hepatitis C
- Epstein-Barr virus
- HTLV
- Human herpes virus 8
- *Schistosoma haematobium*
- *Opisthorchis viverrini*

- High income countries 7.4%
- Low and middle income countries 23% of cancer
- 2 million cases/yr (16%)
  - de Martel et al, Lancet Oncology, 2012
## Medical interventions proven to prevent cancer

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Target</th>
<th>Magnitude of reduction</th>
<th>Time (yrs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>Colon mortality</td>
<td>40%</td>
<td>20+</td>
</tr>
<tr>
<td>SERMs</td>
<td>Breast incidence</td>
<td>40-50%</td>
<td>5+</td>
</tr>
<tr>
<td>Salpingo oophorectomy</td>
<td>Familial breast ca</td>
<td>50%</td>
<td>3+</td>
</tr>
<tr>
<td>Screening for colorectal ca</td>
<td>Colon ca mortality</td>
<td>30-40%</td>
<td>10</td>
</tr>
<tr>
<td>Viruses</td>
<td>Cervical ca incidence</td>
<td>50-100%</td>
<td>20+</td>
</tr>
<tr>
<td></td>
<td>Liver ca incidence</td>
<td>70-100%</td>
<td>20+</td>
</tr>
<tr>
<td>Mammography</td>
<td>Breast ca mortality</td>
<td>30%</td>
<td>10-20</td>
</tr>
<tr>
<td>Serial CT lung</td>
<td>Lung ca mortality</td>
<td>20%</td>
<td>6+</td>
</tr>
</tbody>
</table>
Prevalence of ever having a sigmoidoscopy or colonoscopy (age 50+ ) in Massachusetts

<table>
<thead>
<tr>
<th>Year</th>
<th>Percent aged 50+ ever sigmoid/colonoscopy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997</td>
<td>41%</td>
</tr>
<tr>
<td>1999</td>
<td>44%</td>
</tr>
<tr>
<td>2002</td>
<td>53%</td>
</tr>
<tr>
<td>2004</td>
<td>61%</td>
</tr>
<tr>
<td>2006</td>
<td>66%</td>
</tr>
<tr>
<td>2008</td>
<td>71%</td>
</tr>
<tr>
<td>2010</td>
<td>75%</td>
</tr>
</tbody>
</table>

Source: BRFS
Trend in colorectal cancer death rate in Massachusetts

Source: Naishadham et al, 2011
Trends: CRC mortality

Naishadham et al
CEBP 2011
Huge potential for cancer prevention

• More than half of cancer incidence and mortality could be prevented with what we know now.
• This applies to breast cancer as it does to other major malignancies
Time frame: Where is evidence for prevention in the development sequence of cancer?

• Majority of etiologic studies focus on lifestyle and drugs in proximate time before diagnosis
  ▪ Epidemiology predominantly in postmenopausal women
  ▪ Trials in high-risk women
Time frame: Intervention too late in life

- Genomics, drugs, personalize cancer care
- Prevention exposures just before diagnosis
- Lifestyle interventions in high risk subset of population or in later life
Why are we not preventing cancer now?

Multiple barriers:

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• Short term focus of cancer research
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Key issues: Prevention interventions

- Timing in disease process
- Sustainability of the intervention
  - Dose
  - Duration
  - Durability of intervention after it is stopped/implemented
- Methodological issues
  - Impacting design
  - Interpretation
Timing in disease process

• Where in the disease process are you intervening?
• How long after intervention will benefit be observed?
• What endpoint will be observed?
### Average Timeline from Normal Tissue to Invasive Cancer

<table>
<thead>
<tr>
<th>Age</th>
<th>40 yrs</th>
<th>50 yrs</th>
<th>60 yrs</th>
<th>70+ yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast</strong></td>
<td>Normal or Near Normal</td>
<td>Atypical Hyperplasia</td>
<td>Ductal Carcinoma In Situ</td>
<td>Invasive Cancer</td>
</tr>
<tr>
<td><strong>Cervix</strong></td>
<td>Normal or Near Normal (CIN 1)</td>
<td>Dysplasia (CIN 3)</td>
<td>Carcinoma In Situ</td>
<td>Invasive Cancer</td>
</tr>
<tr>
<td><strong>Colon</strong></td>
<td>Normal or Near Normal</td>
<td>Adenomatous Polype</td>
<td>Invasive Cancer</td>
<td></td>
</tr>
<tr>
<td><strong>Lung (smokers)</strong></td>
<td>Normal or Near Normal</td>
<td>Pre-Cancer</td>
<td>Invasive Cancer</td>
<td></td>
</tr>
<tr>
<td><strong>Pancreas</strong></td>
<td>Normal or Near Normal</td>
<td>Invasive Cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>Normal or Near Normal</td>
<td>Prostate (PRI)</td>
<td>Invasive Cancer</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Figure 11.7, *The Biology of Cancer*, Weinberg (© Garland Science 2007).
Pancreatic cancer

Luebeck EG. Nature 2010
Radiation

• Atomic bomb survivors, 70,165
• 40 year follow-up
• 1059 cases
• Linear increase with radiation dose
• Early age at exposure conveys substantially greater risk

Land et al  Radiation Research 2003
If we conclude that attained age is marker of risk, then:

What does attained age mean?

• Accumulated exposure up to an age?
• Some other function of age?
• Menopause tells us “hormones” or accumulation through premenopausal years must be important
Risk accumulation with age generates other key questions:

• Which lifestyle component to change?
• At what age?
• By how much?
• For how long?
• When will benefit be observed, and how long will benefit last?

See Colditz, Cancer Causes and Control 2010
Colditz and Taylor, Ann Rev Public Health 2010
Model of breast cancer evolution
Wellings-Jensen Model (JNCI 55:231, 1975)

- **TDLU**
  - **↑Growth**
  - **Δs Adhesion & Polarity**
- **CCH**
- **ADH**
- **ALH**
  - **↑Growth**
  - **Δs Adhesion & Polarity**
- **LCIS**
  - **↑Diversity**
- **DCIS**
- **IBC**
  - **Invasion**
- **Time (decades)**
Conclusions: cancer prevention

• Timing matters
• To maximize benefits we must focus on biologically relevant periods
• Address societal factors as well as biology
• Untapped potential for adolescent diet and physical activity for prevention
• We already have many tools for prevention that are not fully used
WHO priorities: population-wide interventions

- Reducing tobacco use (a best buy)
- Promoting physical activity
- Reducing harmful alcohol use
- Promoting healthy diets
- Cancer specific strategies
  - Hepatitis B vaccine (a best buy)
  - HPV vaccine
  - Cervical cancer screening
  - Not currently in low income countries – CRC screening

WHO: Global status report on noncommunicable diseases, 2010
Our societal obligation

- As cancer prevention & control scientists, we must accept responsibility for implementing cancer prevention.
- Prioritize studies that will identify key points for intervention to maximize prevention.
- Move beyond obstacles to implement prevention of cancer here and throughout the world.
Very long term prevention action:

“In the beginning of every enterprise we should know, as distinctly as possible, what we propose to do, and the means of doing it... We desire to lay the foundation and to mature some parts of the plan. Those who come after us must finish the work.”

William Greenleaf Eliot, co-founder
Washington University in St Louis
1854
Thank you

- Bernie Rosner & Cathy Berkey (statisticians)
- Stu Schnitt, Laura Collins, Jim Connolly, Craig Allred (pathologists)
- NHS investigators and trainees and participants
- American Cancer Society Clinical Research Professorship
- NCI & Breast Cancer Research Foundation for funding
Birth Control Pill Use and Risk of Ovarian Cancer

Beral et al, 2008