Clinical Trials and the Minnesota Cancer Clinical Trials Network

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Disclosure

- Clinical Trial Support
  - Boehringer Ingelheim
President Nixon signs the National Cancer Act in 1971. Photo courtesy of the National Cancer Institute.
CANCER UNDEFEATED

JOHN C. BAILAR III, M.D., PH.D., AND HEATHER L. GORNIK, M.H.S.

Conclusions The war against cancer is far from over. Observed changes in mortality due to cancer primarily reflect changing incidence or early detection. The effect of new treatments for cancer on mortality has been largely disappointing. The most promising approach to the control of cancer is a national commitment to prevention, with a concomitant rebalancing of the focus and funding of research. (N Engl J Med 1997;336:1569-74.)

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Cancer Mortality in the US, 1930-2017

Men

Women

Males, by site:
- Stomach
- Colorectum
- Liver & intrahepatic bile duct
- Pancreas
- Lung & bronchus
- Prostate
- Leukemia

Females, by site:
- Stomach
- Colorectum
- Liver & intrahepatic bile duct
- Pancreas
- Lung & bronchus
- Breast
- Uterus (corpus and cervix combined)

Siegel, et al. CA Cancer J Clin 70:7 2020 PMID: 31912902
Cancer Deaths Reduced - 1975-2017

Men

Number of deaths

Year of death

1,983,000 cancer deaths averted

Women

Number of deaths

Year of death

919,200 cancer deaths averted

Siegel, et al. CA Cancer J Clin 70:7 2020 PMID: 31912902
How Did Things Improve?

• Population and laboratory science was applied to patient care
  • Prevention
  • Screening
  • Therapy
  • Survivorship
• Clinical trials
  • Defined new strategies to prevent and screen cancer
    • Adapted to public health policy
  • Identified new treatment targets
    • New drugs developed
  • Reduced “overtreatment” of some cancers
How Did Things Improve?

- Lung cancer
  - Science linked tobacco to DNA damage
  - Public health measures enacted
  - Food and Drug Administration obtained jurisdiction over cigarettes
  - Clinical trials performed to improve
    - Quitting
    - Screening
Tobacco-Specific Nitrosamines: Formation From Nicotine In Vitro and During Tobacco Curing and Carcinogenicity in Strain A Mice

Stephen S. Hecht, Chi-hong B. Chen, Norio Hirota, Raphael M. Ornaf, T. C. Tso, and Dietrich Hoffmann

Vol. 60, No. 4, April 1978

819

J NATL CANCER INST
The Problem With Tobacco

• Nicotine is addictive
• Burned tobacco contains 72 known carcinogens
• Carcinogens in tobacco smoke mutate DNA
• Mutations caused by tobacco are detected in the normal cells and cancers of smokers
A Clinical Trial To Help Smokers Quit

The New England Journal of Medicine

Randomized Trial of Reduced-Nicotine Standards for Cigarettes

Eric C. Donny, Ph.D., Rachel L. Denlinger, B.S., Jennifer W. Tidey, Ph.D., Joseph S. Koopman, Ph.D., Neal L. Benowitz, M.D., Ryan G. Vandrey, Ph.D., Mustafa al'Absi, Ph.D., Steven G. Carmella, B.A., Paul M. Cinciripini, Ph.D., Sarah S. Dermody, M.S., David J. Drobos, Ph.D., Stephen S. Hecht, Ph.D., Joni Jensen, M.P.H., Tonya Lane, M.Ed., Chap T. Le, Ph.D., F. Joseph McClernon, Ph.D., Ivan D. Montoya, M.D., M.P.H., Sharon E. Murphy, Ph.D., Jason D. Robinson, Ph.D., Maxine L. Stitzer, Ph.D., Andrew A. Strasser, Ph.D., Hilary Tindle, M.D., M.P.H., and Dorothy K. Hatsukami, Ph.D.
Study Design

Smokers
N=1250 participants

- Normal Nicotine Content
  15.5 mg/g
  20 weeks
  N=249

- Gradual Nicotine Reduction
  15.5, 11.7, 5.2, 2.4, 0.4 mg/g
  20 weeks
  N=498

- Immediate Nicotine Reduction to 0.4 mg/g
  20 weeks
  N=503

Outcomes
- Patterns of use and exposure biomarkers
- Subjective responses
10 Institutional Sites
Key Findings - Benefits of immediate nicotine reduction

Immediate vs. gradual nicotine reduction and smoking normal nicotine content cigarettes resulted in:

- Greater reductions in cigarettes per day (CPD)
- Greater reductions in nicotine exposure
Key Findings - Concerns about immediate nicotine reduction

Immediate nicotine reduction is associated with:
- Greater withdrawal symptoms
- Higher drop-out rates
- Higher non-compliance with only study cigarette use

Some smokers may need other nicotine products.
A Clinical Trial To Detect Early Lung Cancer

Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial

Lung Cancer (Nederlands–Leuvens Longkanker Screenings Onderzoek [NELSON]) Screening Clinical Trial

- 13,195 men and 2594 women enrolled
- Included: current or former smokers [those who had quit ≤10 years ago] who had smoked >15 cigarettes a day for >25 years or >10 cigarettes a day for >30 years
- Excluded: inability to climb 2 flights of stairs, >300 lbs, past cancer history, recent CT scan
- CT scans at baseline, year 1, year 3 and year 5.5 versus no screening

![Graphs showing lung cancer incidence and mortality](image-url)
**Status Quo**: Lung cancer mortality rates are projected to decrease by ~50% between 2020 and 2040

Projected lung cancer mortality until 2065 – ages 30-84
Means across for CISNET models

<table>
<thead>
<tr>
<th>Projected cancer mortality rates</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Males</strong></td>
</tr>
<tr>
<td>2020</td>
</tr>
<tr>
<td>2040</td>
</tr>
<tr>
<td><strong>Females</strong></td>
</tr>
<tr>
<td>2020</td>
</tr>
<tr>
<td>2040</td>
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</table>
Cancer Mortality in the US, 1930-2017

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- Breast
- Uterus (corpus and cervix combined)

Uterine corpus

Deaths per 100,000 males

Year of death

Siegel, et al. CA Cancer J Clin 70:7 2020 PMID: 31912902
New Therapies For Cancer

- All new and developing therapies are based on laboratory based research
- “Translation” allows strategies developed in the laboratory and preclinical models to be tested in patients
- Clinical Trials go through different phases
  - Phase 1 – “First in human” trials test safety and establish dose
  - Phase 2 – Test dose in single armed trial to establish efficacy
  - Phase 3 – Compare new therapy to standard of care
  - Phase 4 – Post-marketing study to establish “real world” use and safety
New Drugs Take At Least A Decade To Reach Patients

One FDA-Approved Drug - Start to Finish

- 10-15 Years
- 1,000 – 6,000 Volunteers
- $1 Billion

Only 25-30% of Phase 3 trials succeed!!
Things We Knew About Breast Cancer in 1980’s

- Radical mastectomy did not improve survival
  - Clinical trials comparing radical mastectomy versus lumpectomy proved this
- Not all breast cancer were the same
  - Some expressed the estrogen receptor
  - Some spread to the lymph nodes
  - Some patients had good outcomes with surgery alone
- Treatment was the same despite the clinically known heterogeneity
  - Because we couldn’t accurately predict outcome or sensitivity to specific drugs, everyone got the same thing
HER2/neu/c-erbB2 Oncogene

- Rat neuroblastoma used in 3T3 assay and neu identified in 1986.
- Neu related to Epidermal Growth Factor Receptor superfamily - HER2.
- Viral oncogene (avian erythroblastosis virus -erbB) related to EGFR family
- EGFR family members bind to multiple ligands and are transmembrane tyrosine kinases.
HER2 Amplification in Primary Breast Cancer

Slamon et al. Science 235:177 1987
HER2 Amplification in Breast Cancer

Green = Centromere
Orange = HER2

Trastuzumab (Herceptin®) Humanized Anti-HER2 Antibody

- Effective only in HER2 overexpressing or amplified breast cancer
- Synergy with chemotherapy in metastatic disease
- Unexpected cardiac toxicity (CHF) observed in clinical trials
Some Breast Cancers

HER2

Herceptin

Protein

DNA
Trastuzumab (Herceptin®) Improves Outcome in Metastatic Breast Cancer

- ~25% of breast cancers overexpress HER2
- Only HER2+ patients enrolled on this trial
Trastuzumab with Chemotherapy Reduces Mortality in HER2 Positive Operable Breast Cancer

Review: Adjuvant Trastuzumab in the Treatment of HER-2-Positive Early Breast Cancer: A meta-analysis with 9117 patients. (Version 01)

Comparison: 01 Mortality Rate

Outcome: 01 Overall Survival

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Transtuzumab n/N</th>
<th>No transtuzumab n/N</th>
<th>OR (fixed) 95% CI</th>
<th>Weight %</th>
<th>OR (fixed) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCIRG</td>
<td>49/1073</td>
<td>80/1074</td>
<td>0.59 [0.41, 0.86]</td>
<td>20.95</td>
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<tr>
<td>Fin Her</td>
<td>6/116</td>
<td>14/116</td>
<td>0.40 [0.15, 1.07]</td>
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<td>HERA</td>
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<td>NSABP-31</td>
<td>83/864</td>
<td>171/872</td>
<td>0.33 [0.23, 0.50]</td>
<td>42.23</td>
<td></td>
</tr>
</tbody>
</table>

Total (95% CI): 4555 1/4562

Test for heterogeneity: Chi² = 4.93, df = 4 (P = 0.29), P = 16.6%
Test for overall effect: Z = 7.32 (P < 0.00001)
HER2 Story Was Practice Changing

- Laboratory science showed potential vulnerability of cancer cells
- Trastuzumab (Herceptin) was the first monoclonal antibody used for cancer therapy
- Expression of HER2 predicted benefit for HER2-based therapy – precision medicine
- Flipped the significance of HER2 expression in breast cancer – what was identified as a bad sign, transformed into a cancer target
Clinical Trial Participation

- 3% of adults with cancer participate in clinical trials
- 85% of children with cancer participate in clinical trials
  - Acute Lymphoblastic Leukemia
    - 1960’s survival = 0%
    - 2010’s survival = 90%
  - Lack of trial participation slows progress and delays identification of new strategies
Better Survival For Participants In Breast Cancer Clinical Trials

Overall Survival (p<0.00005)

- P = Participate in trial
- C = Guideline compliant
- NC = Guideline non-compliant

1727 women in Quebec
Access to Cancer Clinical Trials

- 42% of Minnesota’s population lives outside the twin-cities metro area (UMN) and greater Rochester area (Mayo Clinic).

MNCCTN aims to improve cancer outcomes for all Minnesotans through greater access to cancer clinical trials in prevention and treatment.
MNCCTN - Overview

- Funded by MnDRIVE in July 2017
  - Ongoing state appropriation

- 5 clinical partner organizations
  - Serve Minnesotans and have experience conducting cancer clinical research

- 18 sites
  - Outside the 7-county metro area and Rochester and had not offered cancer clinical research to patients
MNCCTN - Overview

To improve cancer outcomes for all Minnesotans through greater access to cancer clinical trials in prevention and treatment.
MNCCTN Clinical Trials

- Screening and Prevention
- Treatment
- Symptom Management and Control
- Survivorship

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- Interventional
- Addressing the cancer burden of Minnesotans
  - Lung, Breast, Prostate, Colorectal, Skin
Accomplishments

- 415 people enrolled to 34 clinical trials at 17 sites
- 91 personnel engaged & 26 coordinators hired and trained
- 44 trials are open to enrollment at sites, 34 have enrolled

*as of January 31, 2020
Current MNCCTN Trials

- **GINGER (SPH, UMN)**
  - Impact of Ginger on the microbiome. Can Ginger reduce risk for colorectal cancer?

- **Nicotine Metabolism (MCC, UMN)**
  - Do American Indians metabolize nicotine at a fast rate?

- **Nasal Vestibulitis (Mayo Clinic)**
  - Nasal symptoms in patients starting chemotherapy
  - Surveys with a planned interventional follow-up protocol
Upcoming MNCCTN Trials

- Exemestane (MCC, UMN)
  - Phase II Trial of Exemestane in Previously Treated Post-Menopausal Women with Advanced Non-Small Cell Lung Cancer

- Disulfiram in Patients with Pancreatic Cancer (Mayo Clinic)
  - Can Disulfiram reduce weight and muscle loss associated with pancreatic cancer?

- Rose Geranium (Mayo Clinic)
  - Follow-up to Nasal Vestibulitis
  - Rose geranium in sesame oil to alleviate nasal symptoms
Why Clinical Trials Are Important

- Potential to improve outcomes for patients
- Improvements cannot be made with collaborators (patients)
- Public health and regulatory measures will be based on science obtained from clinical trials
- “Today’s ceiling is tomorrow’s floor”
Advancing Knowledge, Enhancing Care