Reporting Trial Findings in NCI Prevention and Screening Clinical Trials

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Disclosures

I have no financial conflicts to disclose.

The opinions expressed in this presentation are the presenter's own and do not reflect the view of the National Institutes of Health, Department of Health and Human Services, part of the United States Government

Acknowledgement: Patty Spears, Dr. Glenn Lesser

Patients Perspective

Meaningful

+

Relevant

=

Actionable

Intervention Clinical Trials and Participant Consent

Clinical questions (*primary or secondary outcomes*):

- Intervention trials are designed to ask a specific question.
  - Actionable question regarding treating or preventing a specific disease or condition.
  - Trial evaluates a causal effect between intervention and outcome.
- Trial participants are consented knowing these specific questions.

Research questions (*exploratory outcomes*):

- Additional analyses of data and biospecimens collected in the trial.
  - Exploring correlations with clinical outcomes which need confirmation prior to being actionable
- Study participants may have consented to allow their data and specimens to be used for other research but may not be aware of these exploratory questions.

Perspective on NCI-sponsored Cancer Clinical Trials

Cancer treatment trials:

- Historically, many patients with advanced cancer were not alive at the time of trial results.
- As treatment regimens have improved, more cancer survivors want to know the results of the trials and the relevance to their specific scenario.
  - Several NCTN groups have developed trial summaries for patients on study and often will distribute those summaries more broadly as well.
  - Trial results can have nuances such that communicating the results in plain language sometimes can be challenging.

Perspective on NCI-sponsored Cancer Clinical Trials

Cancer prevention and screening trials:

- Large trials with healthy participants who join the trial to contribute and frequently want to know information about the trial.
- Careful thought and effort go into communicating with the study participants from recruitment through the end of the study.
- There are two models:
  - When the data center does not have the participant contact information but relies on the recruitment sites to communicate directly with the study participants. (*NCTN and NCORP model*).
  - When the data center has the participant contact information and is able to reach the study participants directly. (*NLST model*)

NCI-sponsored Cancer Prevention and Screening Trials

End of study, each trial participant receives an end-of-study letter

- Thank you for participation
- Informed that study is ending and the results of the clinical objectives
  - In blinded study, may also provide the assignment to the participant

Study Data Center and NCI coordinate on public announcement

- Assure consistency with language
- Coordinate timing of information to participants with to media release of information
- Study sites communicate with the participants

Specific examples of Cancer Prevention or Screening Trials

- Breast Cancer Prevention Trial (NSABP P-1) with positive finding and offer to participants to receive study drug prior to FDA approval.

- Selenium and Vitamin E Cancer Prevention Trial (SELECT) with no benefit and a non-significant signal for harm and the need to inform participants to stop study drug but continue to be followed on study.

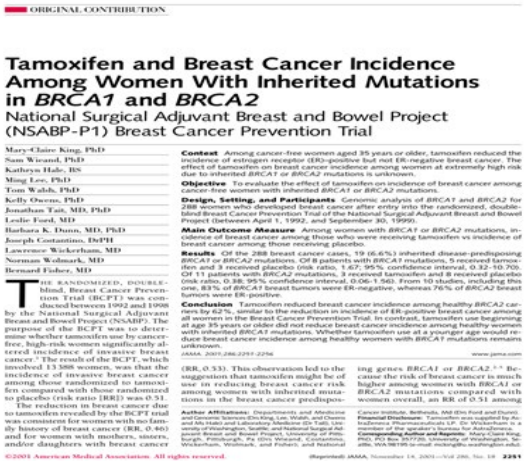
- National Lung Cancer Screening Trial with benefit showed from screening with CT scan.

- One specific example of “closing the loop.”

Breast Cancer Prevention Trial (NSABP-P1)

- Primary endpoint for P1 demonstrated a reduction in the breast cancer incidence across the full study (April 1998)
  - ❖ Actionable results: women in placebo arm could receive tamoxifen at the end of the study
  - ❖ Postmenopausal women could join next trial.

- A research question was whether the risk reduction was also seen in women with mutations in BRCA1 and BRCA2. (2000)
  - ❖ Women did not know their genetic status.
  - ❖ Clinical data linked to biospecimens; BRCA mutation status run on all specimens linked to cancer. Analysis data returned to statistician and no further linkage to participants.



ORIGINAL CONTRIBUTION

Tamoxifen and Breast Cancer Incidence Among Women With Inherited Mutations in *BRCA1* and *BRCA2*

National Surgical Adjuvant Breast and Bowel Project (NSABP-P1) Breast Cancer Prevention Trial

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Context Among cancer-free women aged 35 years or older, tamoxifen reduced the incidence of estrogen receptor (ER)–positive but not ER-negative breast cancer. The effect of tamoxifen on breast cancer incidence among women at extremely high risk due to inherited *BRCA1* or *BRCA2* mutations is unknown.

Objective To evaluate the effect of tamoxifen on incidence of breast cancer among cancer-free women with inherited *BRCA1* or *BRCA2* mutations.

Design, Setting, and Participants Genomic analysis of *BRCA1* and *BRCA2* for 288 women who developed breast cancer after entry into the randomized, double-blind Breast Cancer Prevention Trial of the National Surgical Adjuvant Breast and Bowel Project (between April 1, 1992, and September 30, 1999).

Main Outcome Measure Among women with *BRCA1* or *BRCA2* mutations, incidence of breast cancer among those who were receiving tamoxifen vs incidence of breast cancer among those receiving placebo.

Results Of the 288 breast cancer cases, 19 (6.6%) inherited disease-predisposing *BRCA1* or *BRCA2* mutations. Of 8 patients with *BRCA1* mutations, 5 received tamoxifen and 3 received placebo (risk ratio, 1.67; 95% confidence interval, 0.32-10.70). Of 11 patients with *BRCA2* mutations, 3 received tamoxifen and 8 received placebo (risk ratio, 0.38; 95% confidence interval, 0.06-1.56). From 10 studies, including this one, 83% of *BRCA1* breast tumors were ER-negative, whereas 76% of *BRCA2* breast tumors were ER-positive.

Conclusion Tamoxifen reduced breast cancer incidence among healthy *BRCA2* carriers by 62%, similar to the reduction in incidence of ER-positive breast cancer among all women in the Breast Cancer Prevention Trial. In contrast, tamoxifen use beginning at age 35 years or older did not reduce breast cancer incidence among healthy women with inherited *BRCA1* mutations. Whether tamoxifen use at a younger age would reduce breast cancer incidence among healthy women with *BRCA1* mutations remains unknown.

JAMA. 2001;286:2251-2256 www.jama.com

(RR, 0.53). This observation led to the suggestion that tamoxifen might be of use in reducing breast cancer risk among women with inherited mutations in the breast cancer predispos-

ing genes *BRCA1* or *BRCA2*.[1-3] Because the risk of breast cancer is much higher among women with *BRCA1* or *BRCA2* mutations compared with women overall, an RR of 0.51 among

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Financial Disclosure: Tamoxifen was supplied by AstraZeneca Pharmaceuticals LP. Dr Wickerham is a consultant to AstraZeneca Pharmaceuticals LP.
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(Reprinted) JAMA, November 14, 2001—Vol 286, No. 18 2251

Table 2. Number of Invasive Breast Cancer Cases Among Women by *BRCA1* and *BRCA2* Genotype, Family History, and Age at Diagnosis

Characteristics	No. of Cases				Proportion With Mutation
	BRCA1	*BRCA2*	Wild Type	Total	
First-degree relatives with breast cancer					
None	0	0	58	**58**	0
1	3	4	145	**152**	0.05
≥2	5	7	66	**78**	0.15
Total	**8**	**11**	**269**	**288**	0.07
Age at diagnosis, y					
<50	6	6	57	**69**	0.17
50-59	2	1	110	**113**	0.03
≥60	0	4	102	**106**	0.04
Total	**8**	**11**	**269**	**288**	0.07

SELECT Prostate Cancer Prevention Trial

RCT to determine if Selenium, Vitamin E or the combination would prevent prostate cancer.

- No benefit to prevent prostate cancer
- Possible signal for harm
  - Vit E may increase prostate cancer

- Participants needed to know results prior to announcing broadly
- Participant Advisory Board was key to effectively communicating with participants.

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Vitamins get 'F' in cancer prevention

Updated 1d 22h ago | Comments 66 | Recommend 14 E-mail | Save | Print | Reprints & Permissions | RSS

By Liz Szabo, USA TODAY

Mixx it
Other ways to share:
Yahoo! Buzz
Digg
Newsvine
Reddit
Facebook
What's this?

A flotilla of recent studies — including two papers published today — has sunk the notion that individual vitamin supplements prevent cancer.

With so many earlier studies suggesting that people can eat their way to longer lives, experts acknowledge that their latest findings may leave people confused and even frustrated.

Q&A: Which studies should we listen to?
BETTER LIFE: More on supplements and alternative medicine

"A lot of people are looking at this and asking, 'What happened?' " says Lori Minasian, whose study in today's *Journal of the American Medical Association* found that taking vitamin E or selenium does not ward off cancer.

Enlarge By Tim Dillon, USA TODAY

Vitamin E capsules.

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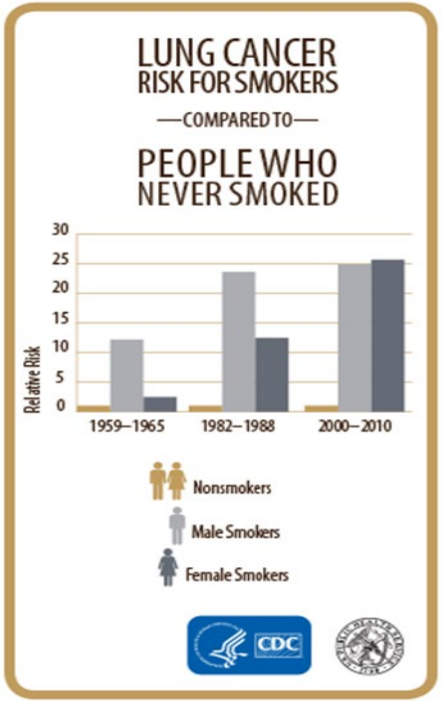
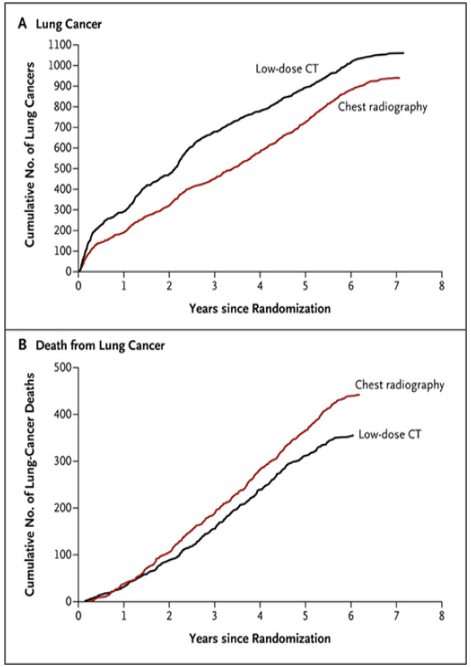
National Lung Cancer Screening Trial NEJM. August 4, 2011

- Randomized trial of Chest x-ray versus Low-Dose CT scan to screen for lung cancer.
- Reduction in lung cancer mortality seen with CT scan
- Letter distributed to all participants providing results of the trial and suggested that those on the Chest X ray arm get a CT scan
- Needed to combine results message with the need to stop smoking.
- De-identified CT scans used in other research projects.





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Example “Closing the Loop” from Dr. Glenn Lesser

- 59 yo female woman with blurred vision and loss of peripheral vision; MRI showed large mass
  - Biopsy diagnosed BRAF V600E mutated craniopharyngioma (*rare cancer*).
- Despite long drives for visits and modest medical literacy, she agreed to participate in a trial.

- Her cancer responded to a BRAF-MEK Inhibitor
- She was seen in follow up on the day the NEJM article was published.
- Rare opportunity to visually and orally share the results of her decision to participate in the trial with the results of the overall trial.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

BRAF–MEK Inhibition in Newly Diagnosed Papillary Craniopharyngiomas

P.K. Brastianos, E. Twohy, S. Geyer, E.R. Gerstner, T.J. Kaufmann, S. Tabrizi, B. Kabat, J. Thierauf, M.W. Ruff, D.A. Bota, D.A. Reardon, A.L. Cohen, M.I. De La Fuente, G.J. Lesser, J. Campian, P.K. Agarwalla, P. Kumthekar, B. Mann, S. Vora, M. Knopp, A.J. Iafrate, W.T. Curry, Jr., D.P. Cahill, H.A. Shih, P.D. Brown, S. Santagata, F.G. Barker II, and E. Galanis

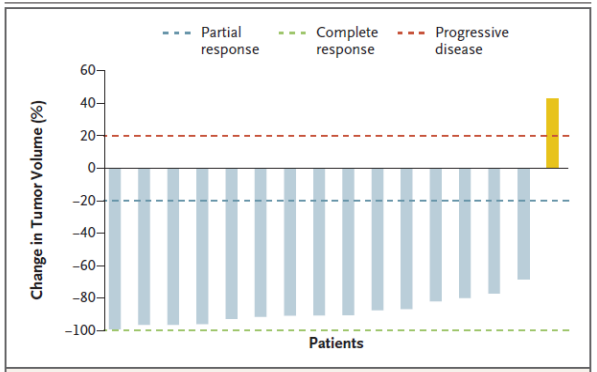

Figure 1. Change in Tumor Volume from Baseline.
The blue bars indicate the 15 patients with papillary craniopharyngiomas who had a partial response to vemurafenib–cobimetinib therapy. The yellow bar indicates 1 patient who received only 8 days of therapy before withdrawing because of toxic effects. The horizontal dashed lines indicate the corresponding measures for each type of response.

Thank you!

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