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DON'T PUT RED, PROCESSED MEAT BACK ON THE MENU: CANCER AND DIETARY EXPERTS DISPUTE CONTROVERSIAL DIRECTIVE

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DON'T PUT RED, PROCESSED MEAT BACK ON THE MENU:

CANCER AND DIETARY EXPERTS DISPUTE CONTROVERSIAL DIRECTIVE

By Matthew Bin Han Ong and Alex Carolan



Global health organizations, federal health agencies, and cancer epidemiology experts say they aren't swayed by just-published recommendations on consumption of red and processed meat.

An international group of researchers earlier this week published five systematic reviews of evidence and concluded that it's okay for adults to continue to eat unprocessed red meat and processed meat at their average consumption levels.

The recommendation, made by the panel of 14 researchers from seven countries and published in *Annals of Internal Medicine* Sept. 30, runs contrary to almost all other existing guidelines.

"Among 12 randomized trials enrolling about 54,000 individuals, the researchers did not find statistically significant or an important association between meat consumption and the risk of heart disease, diabetes, or cancer," a statement from the *Annals of Internal Medicine* reads. "Amongst cohort studies following millions of participants, the researchers did find a very small reduction in risk amongst those who consumed three fewer servings of red or processed meat per week. However, the association was very uncertain."

The lead author of the recommendation paper, Bradley Johnston—who is also a co-founder of the guidelinemaking group, NutriRECS—has previously received funding from the International Life Sciences Institute to conduct a 2016 study on consumption of sugar. ILSI is an industry trade group largely supported by pharmaceutical companies and food companies, including Cargill, one of the largest beef processors in North America.

After news of this conflict of interest surfaced, Johnston argued that his past relationship with ILSI wasn't subject to disclosure and didn't affect the group's recommendations on red and processed meat. The COI subplot of this complex story is developing.

Leading organizations in public health and oncology say the authors' interpretation of findings should not be used to inform public dietary guidelines, because

these new recommendations are "not supported by the scientific evidence."

In six interviews with *The Cancer Letter*, epidemiologists, cardiometabolic scientists, and experts in guidelinemaking characterize the recommendations as "confusing," "sensational," "self-appointed," "so-called guidelines" that are a "disservice to the public."

"Leading global cancer experts do not agree with these authors' interpretation of the scientific evidence," said Jill Reedy, chief of the Risk Factor Assessment Branch, Epidemiology and Genomics Research Program at the NCI Division of Cancer Control and Population Sciences. "[These] cancer experts continue to recommend the guidance that existed before, regarding limiting red meat intake and eating little, if any, processed meat for cancer prevention."

The full transcript of these conversations—with physicians and researchers at NCI, the National Heart, Lung, and Blood Institute, the University of California, San Francisco, MD Anderson Cancer Center, the American Cancer Society, and The University of North Carolina at Chapel Hill—appears on [page 17](#).

These experts, who independently reviewed the studies for *The Cancer Letter*, concluded that:

- The recommendations published in *Annals of Internal Medicine* run counter to the totality and preponderance of evidence, which demonstrates that limiting or reducing consumption of red and processed meats is important for prevention of cancer and cardiometabolic diseases,
- The systematic reviews confirm existing evidence that there is an association between consumption of red and

processed meats with adverse health outcomes, and that

- The investigators should be saying, "We don't know," instead of "Keep going," because the "low to very low" certainty of evidence provided by the systematic reviews is "insufficient" for meeting the threshold for changing or informing dietary guidelines.

"No need to reduce red or processed meat consumption"

Leading up to the publication of the controversial studies Monday evening, reporters around the world received an email with seven PDFs, and an embargoed press release with the headline:

"New guidelines: No need to reduce red or processed meat consumption for good health."

"Based on a series of five high-quality systematic reviews of the relationship between meat consumption and health, a panel of experts recommends that most people can continue to consume red meat and processed meat at their average current consumption levels," the press release from *Annals of Internal Medicine* said.

In summary, the systematic reviews concluded that:

- Low to very-low-certainty evidence suggests that diets restricted in red meat may have little or no effect on major cardiometabolic outcomes and cancer mortality and incidence.
- The possible absolute effects of red and processed meat consumption on cancer mor-

tality and incidence are very small, and the certainty of evidence is low to very low.

- The magnitude of association between red and processed meat consumption and all-cause mortality and adverse cardiometabolic outcomes is very small, and the evidence is of low certainty.
- Low or very-low-certainty evidence suggests that dietary patterns with less red and processed meat intake may result in very small reductions in adverse cardiometabolic and cancer outcomes.
- Low-certainty evidence suggests that omnivores are attached to meat and are unwilling to change this behavior when faced with potentially undesirable health effects.

The authors derived these conclusions based on:

- A systematic review of 12 randomized trials comparing diets lower in red meat with diets higher in red meat, to summarize the effect of these diets on the incidence of cardiometabolic and cancer outcomes in adults,
- Three systematic reviews of 23 cohort studies evaluating the relationship between red meat and processed meat with cancer mortality and incidence, all-cause mortality, cardiometabolic outcomes, quality of life, and satisfaction with diet, and
- A mixed-methods systematic review of values and preferences regarding meat consumption.

The publication packet also included:

- An accompanying editorial from two researchers at the Indiana University School of Medicine endorsing the studies as “the most comprehensive review of the evidence to date,” and
- A paper that states the group’s recommendations.

The final document, titled “Unprocessed Red Meat and Processed Meat Consumption: Dietary Guideline Recommendations,” and labeled “CLINICAL GUIDELINE” in the journal, was developed through a guideline development process created by NutriRECS.

What is NutriRECS?

NutriRECS, or Nutritional Recommendations and Accessible Evidence Summaries Composed of Systematic Reviews, bills itself as “an independent group” of researchers founded by three researchers—an epidemiologist from Canada, a health services researcher from Spain, and another epidemiologist from Poland.

“NutriRECS is an independent group with clinical, nutritional and public health content expertise, skilled in the methodology of systematic reviews and practice guidelines who are unencumbered by institutional constraints and conflicts of interest, aiming to produce trustworthy nutritional guideline recommendations based on the values, attitudes and preferences of patients and community members,” its website states.

NutriRECS receives funding from members’ universities who pay salaries to complete the work, and occasional grants that pay graduate student sal-

aries, said NutriRECS member Gordon Guyatt, Distinguished Professor in the Department of Clinical Epidemiology and Biostatistics at McMaster University, who is an author on all five systematic reviews as well as the recommendations document.

“Our business model is the usual academic model—get your work done by hook or by crook, volunteer labor of folks working for an education and their names on prominent papers, graduate students whose work will be part of their dissertations, and visiting scholars and professors who come to learn how we do things and how to get publications in top journals,” Guyatt said to *The Cancer Letter*.

Several members are also involved in the Cochrane Collaboration of meta-analysts.

A conversation with Guyatt appears on [page 12](#).

A NutriRECS co-founder, Johnston, is intimately involved in the design and development of the studies on red and processed meats published in the *Annals of Internal Medicine*. Johnston is lead author of the recommendation paper, an author on all five systematic reviews, and a corresponding author on four of the systematic reviews.

“One of the gentlemen who did a post-doctoral fellowship with me, Brad Johnston, now works out of Halifax, and I continue to collaborate with him,” Guyatt said. “He has taken a career direction where he wants to focus on nutrition, and particularly on nutritional guidelines, having noted that many nutritional guidelines are not high quality, and are quite flawed, and trust me, the guidelines are necessary.

“We are currently planning our next project, which has to do with fats.”

Sugar, and previous COIs

Though Johnston and his fellow authors of the studies on red and processed meat reported no conflicts of interests, Johnston has received funding from food companies in a December 2016 [study](#) on sugar consumption.

That study, “The Scientific Basis of Guideline Recommendations on Sugar Intake: A Systematic Review,” also published in *Annals of Internal Medicine*, reached similarly formulated conclusions.

Johnston and his team conducted a systematic review of nine public health guidelines on sugar—each suggesting decreasing consumption of foods containing nonintrinsic sugars—including those by the Dietary Guidelines for Americans and the World Health Organization, and concluded that the “quality of evidence supporting [these] recommendations was low to very low.

“Guidelines on dietary sugar do not meet criteria for trustworthy recommendations and are based on low-quality evidence,” the study concluded. “Public health officials (when promulgating these recommendations) and their public audience (when considering dietary behavior) should be aware of these limitations.”

The “low to very low” characterization of the evidence is similarly applied to Johnston and his team’s conclusions on consumption of red and processed meats.

“According to their conflicts of interest, they have none [currently],” Christopher Gardner, director of nutrition studies and Rehnborg Farquhar Professor of Medicine at the Stanford Prevention Research Center, said in an [Oct. 3 interview](#) on KQED San Francisco, NPR’s largest member station. “Two years ago, this same group said there’s no clear evidence that sugar is bad for us, so we

should keep eating sugar at the same amount that we are right now.

“That particular one was funded by ILSI, which is the International Life Science Institute, and that does have some connections to Big Food.

“I haven’t seen big connections to cattle, but in the past this group has done that. I think this one, they tried really hard to be squeaky clean. It’s hard to say for sure,” Gardner said. “So many authors, but they did present clean conflicts of interest statements to the journal.”

Johnston’s 2016 study on sugar was funded by the Technical Committee on Dietary Carbohydrates of ILSI North America. The authors wrote the protocol—the scope of which was reviewed and approved by ILSI—and conducted the study independently from ILSI.

At the time, Johnston was a methods consultant to ILSI, held investigator-initiated grants from BioK+ and Genzyme, and was funded by a joint grant from Nestlé and MITACS Accelerate.

ILSI was created by a Coca-Cola executive in 1978. Members of ILSI have included food companies McDonald’s, General Mills, Nestlé, PepsiCo, and Car-gill, as well as pharmaceutical companies Pfizer and Sanofi.

“The only person with overlap in the two projects was Brad Johnston, who has not taken anything that would constitute a conflict of interest in this one,” Guyatt said. “I don’t know when Brad took the money from this group that has all sorts of food makers in it.

“I think Brad reported his conflict of interest. I think Brad told me that there was somebody in his group who did not [report their COIs on the sugar study].”

One of Johnston’s co-authors in the sugar study, Joanne Slavin, had received laboratory funding from entities that include the Minnesota Beef Council,

Danone, and Coca-Cola. Slavin doesn’t figure as an author on the red and processed meat studies.

A correction added by the *Annals of Internal Medicine* to the 2016 sugar study states:

“Disclosures from two authors (Drs. Johnston and Slavin) were explained in the Disclosures section of the article. The role of the funding source, ILSI, was also clarified in the article and in the Financial Support section.”

The correction was added after the *Associated Press* obtained emails showing that ILSI had “reviewed” and “approved” the study’s protocol, according to *The New York Times*.

“If Brad has managed to get some funding specific to NutriRECS, I haven’t heard,” Guyatt said to *The Cancer Letter*.

Johnston did not respond to emails from *The Cancer Letter*.

“That money was from 2015 so it was outside of the three-year period for disclosing competing interests,” Johnston said to *The New York Times* Oct. 4. “I have no relationship with them whatsoever.”

The International Committee of Medical Journal Editors recommends that investigators report “all sources of revenue paid (or promised to be paid) directly to you or your institution on your behalf over the 36 months prior to submission of the work. If there is any question, it is usually better to disclose a relationship than not to do so.”

The *Annals of Internal Medicine* relies on the ICMJE conflict of interest guidelines.

Johnston should have disclosed his past relationship with ILSI, especially because of the gravity of his group’s recommendations on meat consumption, said Arthur Caplan, the Drs. William F. and Virginia Connolly Mitty Professor of Bioethics at New York University Lan-

gone Health and the founding director of the Division of Medical Ethics.

“If you’re going to try publishing something like ‘smoking doesn’t cause cancer, it’s actually good for you,’ I’d probably try to disclose about 30 years of my past funding of financial relationships,” Caplan said to *The Cancer Letter*. “And meat is very similar.”

In the red and processed meat studies, researchers on the paper disclosed whether they eat red and processed meat and how often they eat it.

“Trustworthy guidelines demand minimizing conflict of interest,” Guyatt said. “So, nobody on our panel had any financial conflict of interest, and we minimized intellectual conflicts of interest. And since some people might perceive what you’re eating as a conflict of interest we declared, as you have noted, the meat in our diet.”

Guyatt said he is a pescetarian, for animal welfare and environmental reasons. The researchers did not include these variables in their guideline development process.

“Considerations of environmental impact or animal welfare did not bear on the recommendations,” the guidelines document states.

Cancer research groups are unconvinced

The NutriRECS recommendations “undermine public confidence in dietary advice,” said Nigel Brockton, vice president of research at the American Institute of Cancer Research.

“We stand by the rigor of our research methodology and our Cancer Prevention Recommendation that people should limit red meat intake to less than 12-18 oz per week and avoid processed meat,” Brockton said in a state-

ment Sept. 30. “The underlying results reported by the NutriRECS group are actually consistent with this advice, but they dismiss these results based on the limitations of some contributing research methods.”

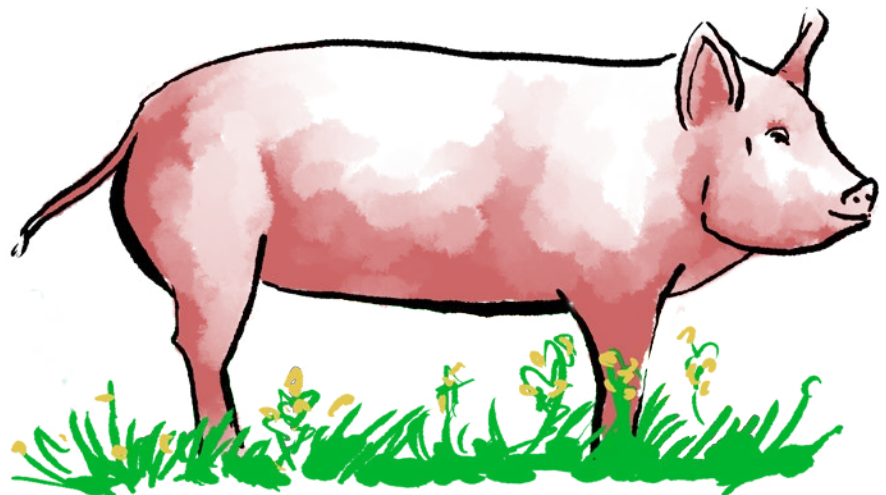
The best available evidence supports an increased cancer risk, AICR said in a statement.

“The NutriRECS research results are not significantly different from what World Cancer Research Fund/American Institute for Cancer Research’s 2018 report found, and indeed seem to verify WCRF/AICR’s findings,” AICR said in a [statement](#). “However, the NutriRECS researchers have made what is a confus-

from NutriRECS is not supported by the scientific evidence.”

The public should continue to use the Dietary Guidelines for Americans, said Holly Nicastro, program director in the Division of Cardiovascular Sciences at NHLBI.

“Dietary guidelines in the United States draw from the same body of evidence that these researchers of the meta-analysis had available to them,” Nicastro said to *The Cancer Letter*. “The difference is that the [Dietary Guidelines for Americans] look at dietary patterns or eating patterns as a whole and conclude that a reduction in red and processed meat would be beneficial. The authors of this



ing interpretation of the results, which has led to this unnecessary recommendation to the public.

“The NutriRECS recommendation does not separate out red and processed meat, and this suggests that three or four portions of processed meat a week do not affect cancer risk significantly enough to warrant a reduction in the amount people eat. This conclusion

analysis looked at red and processed meat in isolation.”

The NutriRECS group weighted randomized trials more heavily than observational studies, which influenced the conclusions of the systematic reviews, critics say.

“Easiest way to think of this report is, a group of people who have exper-

tise in epidemiology got together as a grand jury and they decided to review literature on red meat and processed meat and cancer,” said Otis Brawley, Bloomberg Distinguished Professor of Oncology and Epidemiology and associate director for community outreach and engagement at the Bloomberg School of Public Health and Johns Hopkins Kimmel Cancer Center. “And when you do this sort of thing, you can introduce biases. They openly admit that they down-weighted the importance of non-randomized trials, and they considered randomized trials to be the gold standard.

“And by down-weighting the importance of non-randomized trials, they got

cally said these are far less important than randomized trials in making their decision. These folks came out with the finding that they found because they discounted non-randomized trials, and I don’t think you can discount non-randomized trials because of behavioral considerations.”

The NutriRECS authors have created a “big splash” that is leading to a lot of confusion, said NCI’s Reedy.

“We see that these new so-called guidelines aren’t justified, but keep in mind, these so-called guidelines are also contradicting the evidence that was generated from these authors’ own meta-analyses,” Reedy said. “This was

epidemiology and director of the Bionutrition Research Core at MD Anderson.

“The kind of trial that people want is impossible,” Daniel said to *The Cancer Letter*. “We cannot get individuals to leave everything in their diets the same and just change meat intake and follow them for 10 years to see who gets cancer.

“I’ve worked on studies where we’ve actually found fairly large effect sizes from eating red and processed meat with large prospective studies. It’s individual to the cancer. In colorectal cancer, we’ve seen very large effect sizes. In breast and prostate cancer, we see lower effect sizes, because they’re totally different cancers that develop from totally different mechanisms.

“So, if you mash it all together, the low ones and the high ones, you’re going to get something modest. But that doesn’t mean that red and processed meat doesn’t cause colorectal cancer. From a mechanistic standpoint, it does.”

Public health organizations have accepted that cigarettes are a cause for cancer without needing proof from randomized studies, said Rita Redberg, professor of medicine and a cardiologist at the University of California, San Francisco.

“This reminds me of when the tobacco industry said, ‘No, smoking hasn’t been proven to cause cancer, because there were no randomized studies,’” Redberg, who is also editor of *JAMA Internal Medicine*, said to *The Cancer Letter*. “I mean, you just don’t need randomized studies when you’re talking about big lifestyle issues like smoking or like food.”

To rate the certainty of evidence, the NutriRECS researchers used GRADE (Grading of Recommendations, Assessment, Development and Evaluations), a system typically used in drug trials. Under this grading system, the researchers rated the quality of observational studies as weak

this result,” Brawley said to *The Cancer Letter*. “Now, many people in the community think, for a number of different reasons, that you really can’t just disparage non-randomized trials when you’re asking a question about long-term behavior, like what have you been doing over a long period of time.

“They didn’t exclude non-randomized trials, they actually just mathemati-

a self-appointed panel, and I know that we’ve heard from other reports that there is some disagreement among the authors. Not all the authors agreed with the language and the final papers.”

Lifestyle factors, including diet, are difficult to study in randomized clinical trials, which would require tracking eating habits over many years, said Carrie Daniel-MacDougall, associate professor of



or very weak, said Marji McCullough, senior scientific director of epidemiology research at the American Cancer Society.

“In reviewing the evidence for diet and lifestyle, we tend to use different review criteria, because it’s really difficult to do long-term trials of diet and cancer,” McCullough said to *The Cancer Letter*. “They would downgrade the evidence if there weren’t repeated measures of diet during the course of a prospective analysis. And they would downgrade if, for example, family history was not included in the model.

“The American Cancer Society continues to recommend that people limit their consumption of unprocessed red meat, and especially processed meat, based on the totality of the existing evidence and conclusions by the World Health Organization that processed meats are carcinogenic and unprocessed red meat is considered a probable carcinogen.”

Evidence-based medicine based on low-certainty data

Because Guyatt, Johnston, and their team found “low to very low” certainty of evidence, and the magnitude of effect of red and processed meat consumption on cardiometabolic and cancer outcomes is small, are the recommendations to maintain consumption levels reasonable?

Evidence-based medicine is the practice of using the best available evidence to make decisions, according to Guyatt, who says he coined the phrase “evidence-based medicine.”

“Well, you have to make choices, right?” Guyatt said. “We don’t say, ‘No, sorry. No randomized trials, can’t help you.’ Instead, we use the best evidence available.

“This is certainly not ideal to have only low-quality evidence, but people need

to make decisions about their red meat consumption, and the decisions should be based on the best evidence available.”

Russell Harris, emeritus professor of the Public Health Leadership Program at The University of North Carolina at Chapel Hill, disagrees.

“What [NutriRECS] could have said is, ‘The evidence is insufficient,’” Harris



The kind of trial that people want is impossible. We cannot get individuals to leave everything in their diets the same and just change meat intake and follow them for 10 years to see who gets cancer.

— Carrie Daniel-MacDougall



said to *The Cancer Letter*. “They could say, ‘This evidence is so lousy that we can’t tell you whether eating meat is bad. Certainly, there’s no signal here that it’s good for you, by the way. But we can’t tell you whether it’s bad for you or not. So, you’re going to have to decide this based on other things.”

Harris is a former member of the United States Preventive Services Task Force, an independent, volunteer panel of national experts in disease prevention and evidence-based medicine. The Centers for Medicare and Medicaid Services use USPSTF recommendations to inform coverage.

“Let me point out, that’s the reason the [Task Force] has what they call an ‘I,’” Harris said. “They’re one of the only guideline groups that have something called an ‘I,’ insufficient evidence—that means we looked at the evidence as hard as we could.

“And guess what? This doesn’t answer the question that we wanted to ask.”

The NutriRECS authors may be “calling out” others who have made strong recommendations on the consumption of red and processed meat, Harris said.

“To me, they made the same mistake that they’re calling others out for having made. That’s an error,” Harris said. “Is the evidence enough to make a

recommendation? That’s really where we are with this. Is there enough evidence here to say anything other than, ‘I don’t know?’”

Daniel and Redberg said they continue to recommend a Mediterranean-style diet.

“I think something in the paper that was sort of buried was the dietary patterns that are traditionally lower in red and processed meats, like the Mediterranean diet,” Daniel said. “The Mediterranean diet has been associated—in several studies and trials—with lower risk of cancer and cardiovascular disease.

“Overall, eat a variety of foods, but not too much. That has not changed just because a paper has come out on this.”

“I like what Michael Pollan said, ‘Eat food. Not too much. Mostly plants,’” Redberg said. “And get regular exercise.”

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Guyatt spoke with
Matthew Ong and Alex Carolan,
reporters with
The Cancer Letter.

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CONVERSATION WITH
THE CANCER LETTER

Guyatt: Existing dietary guidelines for red and processed meat are based on slim evidence and are paternalistic

“

Evidence-based medicine is using the best available evidence to make decisions, because you need to make decisions. And the same is true here.

”



Gordon Guyatt
*Distinguished Professor,
Department of Clinical Epidemiology and Biostatistics,
McMaster University*

The senior author of the recent recommendation that disagrees with the dietary guidelines promulgated by mainstream health organizations said there is low-certainty evidence of increased risk of cancer, heart disease, and other harm from eating red meat and processed meat.

“There is low-quality evidence of a small effect. To us, it is presumptuous and paternalistic to tell people, on the basis of low-quality evidence of small effects, that they should cut down on eating their red meat,” said Gordon Guyatt, distinguished professor at the Department of Clinical Epidemiology and Biostatistics at McMaster University.

“Some people may well, on the basis of that evidence, choose to do so, but we think a majority of people would not. And it’s hard to imagine anybody claiming that all or almost everybody, on the basis of low-quality evidence of small effects, given people’s quality of life enhancement when they eat meat, that everybody would choose to cut down their stuff.”

Guyatt, the scientist credited with coining the term “evidence-based medicine,” said no mainstream health organizations have contacted him directly after his group’s paper was published in the *Annals of Internal Medicine*.

“From what I understand—which I mainly heard secondhand from the porch, from my colleagues—the organizations that have previously said, ‘Death awaits you if you continue to eat red meat,’ have not been terribly positive,” Guyatt said.

Guyatt spoke with Matthew Ong and Alex Carolan, reporters with *The Cancer Letter*.

Matthew Ong: So, doctor, may I have a smoked kielbasa tonight? How about a hamburger?

Gordon Guyatt: That is a matter of your values and preferences. So, the situation is that there is low-quality evidence suggesting that your hamburgers may, if you continue to eat them on a daily basis or regularly, increase your risk of cancer and increase your risk of cardiovascular disease.

But if it does increase it, and it may not, because the evidence is only low-quality, the increase will be a very small increase. So, it’s up to you. How much does the hamburger appeal to you and how much are you ready to give up to avoid a small and uncertain harm?

MO: And the same applies to the kielbasa?

GG: That’s correct.

MO: So, what led you and your team to perform these studies?

GG: Well, one of the gentlemen who did a postdoctoral fellowship with me, Brad Johnston, now works out of Halifax, and I continue to collaborate with him.

He has taken a career direction where he wants to focus on nutrition, and particularly on nutritional guidelines, having noted that many nutritional guidelines are not high-quality, and are quite flawed, and trust me, the guidelines are necessary.

I continue to collaborate with him, and he has asked me to be part of his team, having decided to take on red and processed meat as the first of his nutritional guidelines.

MO: Are you planning on conducting systematic reviews of all major nutritional and dietary guidelines going forward?

GG: Well, I don’t know if we’ll ever get to all of them. However, we are currently planning our next project, which has to do with fats.

Alex Carolan: Could you briefly describe your findings from your systematic reviews? Also, why are these findings important to public health?

GG: So, what our findings suggested is that there is only low-quality evidence available linking red and processed meat with cancer and cardiovascular outcomes.

However, that low-quality evidence does suggest a possible causal connection between meat consumption and cancer and cardiovascular risk.

However, even if there is a true causal relationship, and there may not be, the impact over a lifetime would be quite small of continuing to eat red meat. That is, the health adverse outcomes will occur very infrequently.

To put it the other way around, decreasing your red meat, even if the causal connection is true, and it may not be, would lead to only a small reduction in risk.

Anything that might have an impact across the population—clearly, everybody has to eat, and, clearly, lots of people eat red meat—so, anything that is an issue across the whole population or influences a whole population may be relevant for public health.

AC: I noticed that everyone who participated disclosed how much meat they eat a week, and I think I saw that you are a pescetarian.

GG: Yes. That is correct. So, to clarify that, I am not a pescetarian for health reasons. I am a pescetarian because of animal welfare and environmental reasons. And maybe I shouldn't even be eating fish, but I still do.

AC: Could you walk us through the methodology for your studies?

GG: So, over the last 20 years, there have been standards for doing what we call trustworthy guidelines. And the standards include who you have on the panel.

So, nowadays, you'd like to include, as we did, people who are expert in nutrition, people who are expert in interpreting the literature—we call them methodologists, people like me—and patients, if it's a medical condition; in this case, people from the community. So, we included all of those groups in our panel.

Second, trustworthy guidelines demand minimizing conflict of interest. So, nobody on our panel had any financial conflict of interest and we minimized intellectual conflicts of interest. And since some people might perceive

what you're eating as a conflict of interest, we declared, as you have noted, the meat in our diet.

A third element of trustworthy guidelines is up-to-date systematic reviews of the best evidence. So, we conducted what we believe is often state-of-the-art methodology in conducting systematic reviews of red and processed meat for cancer, red and processed meat for cardiovascular disease, dietary patterns and cancer and cardiovascular disease, and those were all observational studies, reviews.

We also did a systematic review on the randomized trials that have addressed the potential impact of meat consumption on health outcomes.

And finally, since this is, we believe, a value and preference-sensitive decision about meat, we conducted a systematic review of studies that had addressed people's values and preferences with respect to meat consumption. So, those five systematic reviews—hopefully, we believe, done under the most rigorous, up-to-date standards—informed the guideline.

MO: Some critics say that the meta-analyses place more weight on results from randomized trials, over that of observational studies, which was how your team derived the published conclusions.

GG: Untrue. We concluded that the randomized trials also only provide us with low-quality evidence.

The randomized trials suggested there is no relationship between red and processed meat and health outcomes. In fact, when we presented our summaries and our best estimates of the magnitude of effect—as it turns out, a very

small magnitude of effect—we based those on the observational studies.

MO: Others have said that it would have been important for you to make conclusions for red meat and processed meat separately. Could you respond to that as well?

GG: We did. If you look at our summaries, he makes separate summaries for red and processed meat. The magnitude of the associations were consistently a little bit higher with processed than with red meat.

MO: Some experts say that they are a little suspicious of these recommendations, because some authors on your team published an article two years ago, concluding that eating more sugar is fine, and received funding from food companies, according to critics. Is this true?

GG: First of all, and the statement was not that eating sugar was fine. I should say I was not a coauthor on that paper, but I was acknowledged, because I gave them advice, so I know what was in it. It was that the guidelines were flawed, which are two very different things.

Second, the only person with overlap in the two projects was Brad Johnston, who has not taken anything that would constitute a conflict of interest in this one.

I don't know when Brad took the money from this group that has all sorts of food makers in it, but it was more than three years ago. The conflict of interest about

funding is accurate for the stated time period. I think Brad reported his conflict of interest.

I think Brad told me that there was somebody in his group who did not. As I say, I only gave them some advice in it. But anyway, you'd either have to talk to Brad or look back at the paper.

What I can say with confidence is that our reports have no conflict of interest in the current situation.

MO: You mentioned that the guidelines on consumption of sugar were flawed. Could you briefly describe the framework for that?

GG: Once again, I was not an author in the paper. With all those limitations, typically they would not have done a comprehensive search.

They would not have followed the most rigorous guidelines. In particular, they would not have used grade, and they would have paid little attention to people's values and preferences. They would not have summarized their results in summary findings, tables, or evidence profiles.

Now that, frankly, is not by my memory. This is just what I would've expected, because then these are the limitations that have tended to be the case in nutrition guidelines.

MO: So, it appears many of our readers are not familiar with NutriRECS. What is NutriRECS, and what is your business model? Also how is the organization funded?

GG: If you Google NutriRECS, you can find out all you want to know about the group. Our business model is the usual academic model—get your work done by hook or by crook, volunteer labor of folks working for an education and their names on prominent papers, graduate students whose work will be part of their dissertations, and visiting scholars and professors who come to learn how we do things and how to get publications in top journals (Miah Han on the red meat and cancer paper is a good example of the last of these).

If Brad has managed to get some funding specific to NutriRECS, I haven't heard. So, it's effectively in-kind funding from the universities that pay our salary to do this work, and the sources above (sometimes, we get grants to pay grad students' salaries).

MO: Your team's recommendation, as it appears, is that everyone should continue consuming red meat and processed meat at current levels. Please correct me if I am mistaken.

GG: First of all, a slight misstatement in what you said. We did not say everybody should continue their red and processed meat consumption.

We said that it should be an informed decision, and our guess is that the majority of people who were fully informed of the evidence would choose to continue their red and processed meat consumption, but that a minority—perhaps a sizeable minority—when fully informed would choose to reduce.

So, we're not telling you that everybody should continue. We're saying that it should be a fully informed decision, and our guess is that, when fully informed, the majority of people would choose to continue. We could be wrong.

Perhaps the majority of people would choose to reduce. But that was our guess, that the majority would choose to continue. And that's why we made that weak recommendation. So, that's the slight correction from the way you put it.

MO: If the evidence is of low certainty, if the magnitude of effect is small, and if the absolute risk is low, do you consider the evidence sufficient for informing guidelines?

GG: Well, you have to make choices; right? People either choose to eat red meat, increase their red meat, decrease their red meat, whatever. Okay?

And I'll make a little parody of evidence-based medicine, which we try to put into practice.

A patient comes to see the physician and says, "Oh, I got this problem. Doctor, can you help me?"

Doctor turns to the computer, spends a few minutes on the computer, turns to the patient and says, "Sorry, I can't help you. No randomized trials."

That is not evidence-based medicine. So, evidence-based medicine is using the best available evidence to make decisions, because you need to make decisions. And the same is true here.

This is certainly not ideal to have only low-quality evidence, but people need to make decisions about their red meat consumption, and the decisions should be based on the best evidence that is available.

Unfortunately, in this case it's only low-quality, but we should look at the best evidence available and, considering the limited quality, make our decisions accordingly.

MO: I see that you're credited with coining the phrase "evidence-based medicine." What's the story?

GG: Well, in 1990, I took over the residency program in internal medicine at McMaster University in Hamilton.

And we had a basic notion of what we wanted to do, which is that we wanted to train a new breed of physician who would pay much closer attention to the evidence, would have a much deeper understanding of the nature of medical evidence and use that to optimally manage their patients.

And we wanted to attract people to McMaster who might be interested in that approach. And the approach needed a name.

So, my first go at coming up with a name was "scientific medicine," which so outraged my colleagues that I decided I'd better go back to the drawing board.

And my second choice was "evidence-based medicine," which ended up being extremely popular.

AC: What sorts of responses have you received so far to your team's papers from mainstream health organizations?

GG: Well, no mainstream organizations have contacted me directly.

From what I understand—which I mainly heard secondhand from the porch, from my colleagues—the organizations that have previously said, "Death awaits you if you continue to eat red meat," have not been terribly positive.

MO: You've addressed some of the following, but I want to make sure to condense it. The statements I've received in response to your recommendations appear to range from A) the totality and preponderance of evidence gathered so far continue to point to the importance of limiting or reducing consumption, to B) these systematic reviews show that there is insufficient evidence to inform guidelines, so the investigators should be saying "We don't know." What is your response to both of these statements?

GG: With respect to the first one, we disagree. So, there is low-quality evidence of a small effect.

To us, it is presumptuous and paternalistic to tell people, on the basis of low-quality evidence of small effects, that they should cut down on eating their red meat.

Some people may well, on the basis of that evidence, choose to do so, but we think a majority of people would not.

And it's hard to imagine anybody claiming that all or almost everybody, on the basis of low-quality evidence of small effects, given people's quality of life enhancement when they eat meat, that everybody would choose to cut down their stuff.

So, the first is a mischaracterization of the evidence and, in my personal view, a paternalistic or parental approach.

Instead of giving people the evidence and letting them make their decisions, telling them what to do on the basis of this evidence, to me is quite problematic.

With respect to the second statement, you're quite right. That's what I just dealt with. It would be absolutely wrong for doctors to say, "Oh sorry, not enough evidence. Can't advise you."

As a matter of fact, most of what we do in medicine, sadly enough, is still low-quality evidence. And that goes back to the parody of evidence-based medicine that I just gave you.

We don't say, "No, sorry. No randomized trials, can't help you." Instead, we use the best evidence available. And, in my opinion, it is quite informative to tell a person who is inquiring, "Oh sorry, we only have low quality evidence that red and processed meat may be causing increases in cancer and cardiovascular risk, but it may not. We're not sure. And if it does, the increases in risk are small." That strikes me as very informative.

MO: I believe our sources so far appear to agree that number one, your findings in these systematic reviews are in line with existing evidence, in the sense that yes, it is low-quality evidence, but nevertheless, there is an association between consumption and adverse health outcomes. And number two, certainly, that there is no positive recommendation, based on the evidence, to increase consumption. Are these statements accurate?

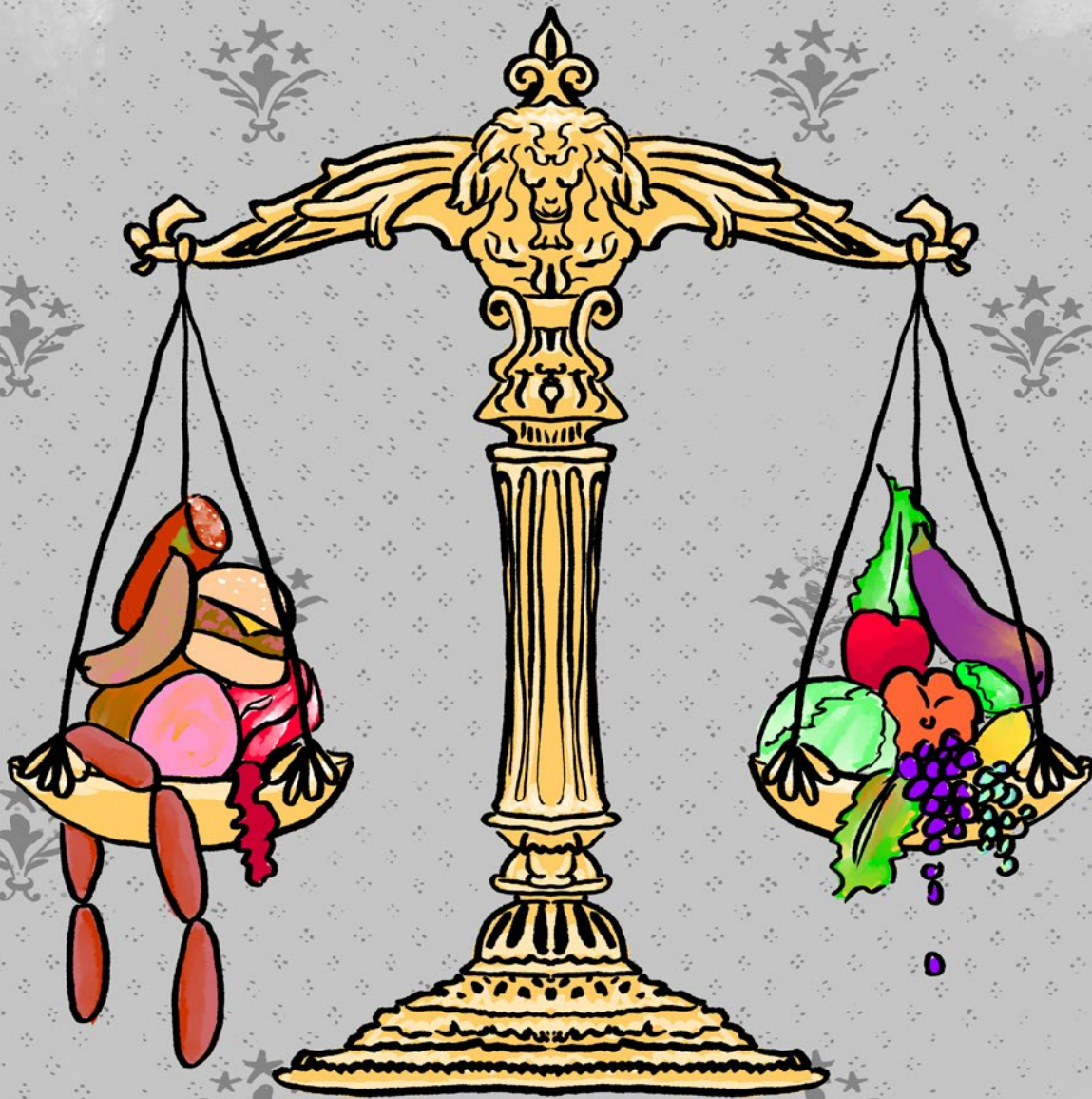
GG: Those are both accurate. The only qualification would be, although we and other people focused on the observational studies—they're limited, but one should perhaps not dismiss completely the randomized trials, which suggest no association.



Should you eat a kielbasa tonight?

CONVERSATION WITH
THE CANCER LETTER

SIX EXPERTS WEIGH EVIDENCE
ON PAPERS DEBUNKING
NUTRITIONAL GUIDELINES ON
RED AND PROCESSED MEAT





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We asked six experts in disease prevention, nutrition, and guideline-making to discuss the just-published recommendations that disagree with the dietary guidelines promulgated by mainstream health organizations.

The [paper](#), published in *Annals of Internal Medicine* said there is little evidence of increased risk of cancer, heart disease, and other harm from eating red meat and processed meat.

The *Cancer Letter* reporters Matthew Ong and Alex Carolan asked all six experts the same 10 questions.



So, doctor, may I have a smoked kielbasa tonight? How about a hamburger?

Reedy, NCI: Let's talk more about you and your overall eating pattern, as well as what makes up a healthy eating pattern. Then, you can consider how those foods may or may not work for you. Leading global cancer experts continue to recommend the guidance that existed before, regarding limiting red meat intake and eating little, if any, processed meat for cancer prevention.

Nicastro, NHLBI: I won't physically try to stop you from eating your smoked kielbasa or hamburger. I'll just remind

you that current Dietary Guidelines for Americans encourage a healthy diet that is high in vegetables, fruits, whole grains, low and nonfat dairy, seafood, legumes and nuts, and limits red and processed meats, sugar-sweetened foods and drinks, and refined grains.

Redberg, UCSF/JAMA: These studies don't change my advice. In general, smoked foods have some carcinogens and other things. So, you should limit your intake. If you want to have it to-night, I think once a week, once every two weeks, once every few weeks is fine. But I wouldn't have it every night.

Daniel, MD Anderson: Well, maybe you can have one tonight, but then I would suggest not having some again for a while. I feel that we are not ready to change dietary recommendations based on a single report. That's not how things work. Whether their report is right or wrong, it's still one report from one group and that's not how we make changes and decide what's important for public health.

McCullough, ACS: Kielbasa is OK if you eat it only occasionally. One suggestion is to use small amounts to flavor a dish, instead of considering it the center of your meal. A hamburger is a fine alternative, but you should limit your total red meat consumption to a few times per week or less. Be sure to choose lean cuts, and avoid charring or burning your meat. And be sure to load up on veggies.

Harris, UNC: If you are thinking about whether these things will affect your health, we really don't know the answer to that very good question. If you have it once, the likely answer is that it will neither help nor hurt. If you eat it regularly, we really don't know.

If you want to know whether regular eating of these meats will cause environmental damage compared with eating vegetable protein, the answer is yes, these meats are worse for the environment than eating vegetable protein.

Is this the first time that a comprehensive meta-analysis of health outcomes of this kind—stemming from consumption of red meat and processed meat—has been conducted?

Reedy, NCI: A review by the International Agency for Research on Cancer of the World Health Organization was released in 2015. Most recently, in 2018, the Third Expert Report came out from the American Institute for Cancer Research and the World Cancer Research Fund. These dietary guidelines review specific questions related to dietary patterns and the role of red and processed meat. So, yes, there are other reviews of this kind.

Redberg, UCSF/JAMA: No, not at all. There have been multiple meta-analyses. We published several, and when I say "we," I mean *JAMA Internal Medicine* in the last few years. I think our most recent one was from the French group NutriNet-Santé, looking at processed foods, organic food and meat consumption. That was a study, not a meta-analysis, but there have been multiple meta-analyses published, and all of them find that diets that are low in red and processed meats are associated with longer life.

Daniel, MD Anderson: It's not the first time by any stretch of the imagination. They just did it differently. And when you use different methods, you're going to get slightly different answers.

What's really different about this review versus prior reviews is this group is really looking at the perspective of individual decision making, and they're looking at broader cancer outcomes, where they've melded different cancers together. The way that they weigh evidence is different, and so, they're getting slightly different answers. I'm



We are not ready to change dietary recommendations based on a single report. That's not how things work. Whether their report is right or wrong, it's still one report from one group and that's not how we make changes and decide what's important for public health.

—Carrie Daniel-MacDougall



not saying that one is a better way or one is not a better way, but they're just incredibly different. And for cancer, I don't find this review as convincing as others that I have seen.

McCullough, ACS: Meta-analyses similar to these have been conducted before. And I think these meta-analyses are consistent with relative risks of these various outcomes that have been shown previously. In that regard, the findings are very consistent with previously conducted meta-analyses and systematic literature reviews.

Harris, UNC: I'm not an expert in this area, though I have looked at it in some cases before, but from all I know and from all I can read, they really surveyed the literature really well. They got all the studies, they put them all together, and they are correct, I think, that the certainty of evidence of association is either low or very low.

Although the other side of the coin, as I was saying, I think what Dr. Hu at Harvard and others would say is that "Yes, the evidence is not great, but what evidence there is—and there are a lot of studies, all of which are flawed—all of them seem to show basically the same thing, with some exceptions, that there is an association."

It's just that we're not real sure about it, because there could be other things that might explain that association. But consistency is one of the things that is important here.

What are your takeaways from these systematic reviews?

Reedy, NCI: The key takeaway is that we know that leading global cancer experts don't agree with these authors' interpretation of the scientific evidence. These are so-called guidelines.

In nutrition science, as in all areas of research, scientists examine and evaluate the literature, and produce reports where there is concurrence and where research gaps remain. In the Dietary Guidelines for Americans, nutrition experts come together every five years to review the scientific evidence and write scientific reports. Those guidelines are in process right now and being updated. But the existing guidelines haven't changed in light of these so-called guidelines that have been released.

Nutrition experts have also reviewed the literature specifically for cancer, through the efforts led by the American Institute for Cancer Research and the World Cancer Research Fund—they published their Third Expert Report in 2018. We also have the World Health Organization's International Agency for Research on Cancer's monograph on red meat and processed meat. These reports align—the Dietary Guidelines, the AICR/WCRF Report, and IARC's monograph.

Nicastro, NHLBI: Our takeaways are that the current United States Dietary Guidelines for Americans still stand—the overall recommendations about a healthy dietary plan of a variety of fruits and vegetables, and protein foods, etc. The guidelines are based on a high quality of evidence, and that is what we should be putting forth to the public.

Redberg, UCSF/JAMA: We already knew we don't have a lot of randomized controlled studies when it comes to nutrition, but I don't think that we should expect to have randomized controlled studies. It's not reasonable when you're talking about food, which is certainly a lifestyle, and not a drug, where you could easily randomize and give half the people the drug and half the people control.

We all eat different things, and we're very complex. I think of food research like smoking research. To me, this reminds me of when the tobacco industry

said, “No, smoking hasn’t been proven to cause cancer, because there were no randomized studies.” I mean, you just don’t need randomized studies when you’re talking about big lifestyle issues like smoking or like food.

There have been so many very large observational studies that show, convincingly and consistently, that people who eat more of a plant-based diet live longer and have better quality of life. To take that same data and then say, because “there are no randomized studies,” that we think it’s fine to eat meat every day, I think does a disservice to the public.

Daniel, MD Anderson: So, I actually would refer you to the American Institute of Cancer Research and the World Health Organization, particularly for your readers, if you want to know a group that for several decades has been putting together expert panels to go over the literature. I’m talking human evidence, observational and trial and experimental evidence; for example, how does this work in a mouse? How does this work in different types of model systems? What is the impact on the microbiome?

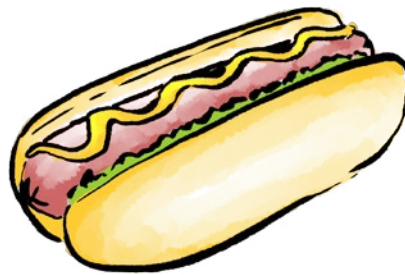
The AICR and WHO have two different panels that get together. One is composed of people who have expertise in human nutrition with expertise in nutritional epidemiology or clinical trials. Then they have another group that gets together who is more basic science, and together they review all the experimental evidence on each of the topics.

The other thing that’s critical to note is that these groups (the AICR and WHO) look at individual cancers and even subtypes within those cancers. So, for example, we know that esophageal cancer has two very distinct subtypes and diet is only related to one of those subtypes. And they look at that level of detail at the literature and at the evidence before they make their statements and conclusions.

McCullough, ACS: As I mentioned, these authors actually confirm what’s been reported before in terms of the relative risk. They also present the evidence based on the risk difference. The risk difference for cutting back on or limiting red or processed meat may appear small for some of these outcomes. For others, it’s really how you interpret it.

But while they might seem small for some of these outcomes, for individuals who eat a lot of meat or might have a family history of a particular outcome, it might have more of an impact.

What they’re saying is that on an individual basis, if an individual is to look at this and say, “How much can I lower my risk of different outcomes, would this make a big difference for me?” For some, the risk difference on an individual level is small.



In the example I cited before, the authors estimated that the lifetime risk of dying from cancer was 105 per 1,000 people, that number goes down to eight fewer with lowering processed meat intake. So, instead of 105, it would be 97.

Regarding Table 2 in their paper on cancer mortality, an individual could look at this and say, “Well, my lifetime risk is already 105, but if I cut back by three servings of processed meat per week, then that would be 97.” For an absolute risk difference, that’s how it translates for an individual. Individuals could weigh this information to decide

whether it’s really worth it for them to limit their intake.

But in addition, these authors also published a narrative review on a summary of studies that have looked at people’s meat preferences, and whether they would be willing to cut back on their meat intake. And they concluded that omnivores would be unlikely to want to cut back on meat intake. In their recommendations, they considered that people are unlikely to change their habits.

Harris, UNC: There are a couple of things that are important in writing about this. Make sure that you keep two things separate. One is the certainty of the evidence, and here, it’s the certainty of evidence of association. Whether or not that association is causal or not is a separate question, but the certainty of evidence of association is the first issue.

The second issue is the magnitude of effect. And that magnitude of effect may be looked at in absolute terms or relative terms. Usually, people look at it in relative terms if they want to make it look big, but absolute terms, I think, would be more informative.

What these folks have done is five systematic reviews, and these are very good people, let me just say. These are not rookies or amateurs. These guys know what they’re doing. So, they have done an exhaustive search of the literature with thousands of papers. I mean, we do these systematic reviews ourselves here at UNC for the [US Preventative Services] Task Force, and it takes us 18 months. It looks like it took them several years to do this. And I’m not surprised. And so, they’ve done an exhaustive search of literature, and they have looked at, first, certainty, they say, for almost every category, except for people’s opinions.

The other systematic reviews find either low or very low certainty. That’s not uncommon in systematic reviews. We often see that. So, we, methodologists,

look at evidence fairly critically these days. And so, it doesn't look like the evidence is very certain about whether there's an association or not. If anything, it falls on the side of association. It's just that the evidence is not real good about that association.

But, in all fairness, I think the people like Frank Hu at Harvard, they would point out that it's pretty consistent that it is a positive association. It's just that the evidence is not real strong about that.

And that has to do with all kinds of methodologic problems with nutritional epidemiology, which we can go into, if you want. But other people have talked about that before—unmeasured confounders and whether measurement itself is good, and whether the time is adequate to look at these things.

Are the conclusions presented in these systematic reviews consistent with what you know about evidence on the association between consumption of red and processed meats with cardiometabolic and cancer mortality outcomes?

Reedy, NCI: The authors have really created a big splash, and unfortunately, it's leading to a lot of confusion. We see that these new so-called guidelines aren't justified, but keep in mind, these so-called guidelines are also contradicting the evidence that was generated from these authors' own meta-analyses.

They have five published systematic reviews, and in three of these meta-analyses, they're reporting similar findings as other reviews on red and processed meat and increased risk for specific health outcomes. These studies are all finding that a lower consumption of red meat and processed meat is associated with the reduced risk for all cause

mortality, for cardiovascular mortality, for cancer mortality, and for Type 2 diabetes.

Nicastro, NHLBI: The authors' recommendations from the meta-analysis were considered weak recommendations in citing low certainty of evidence. So, this suggests the authors are equivocal in their recommendations. The recommendations also were not unanimous in the paper.

Current Dietary Guidelines in the United States draw from the same body of evidence that these researchers of the meta-analysis had available to them. The difference is that the guidelines look at dietary patterns or eating patterns as a whole and conclude that a reduction in red and processed meat would be beneficial. The authors of this analysis looked at red and processed meat in isolation.

Redberg, UCSF/JAMA: The evidence here, to me, says the same as all the evidence I've read in the past, that there is good epidemiologic data to suggest that there is better survival with less meat-based diets. I think what they're saying is that the quality of the evidence is low. But as I said, I don't think that you can expect to have randomized trials when you're talking about nutrition.

Besides, there have even been nutritional trials like the Lyon Heart study and the PREDIMED study that looked at a Mediterranean diet versus a low-fat diet. I think that, in those cases, they were low-fat diets, and found health benefits. There have been some randomized studies for eating habits. Those are definitely fewer, as I said, but I think that's because it's very hard to randomize people. You can't put people in a lab and expect they're going to eat a prescribed diet for any period of time. It's not reasonable.

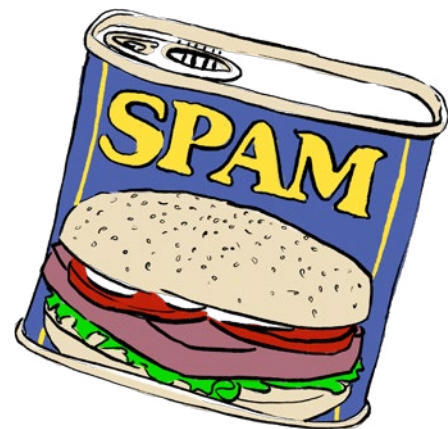
Daniel, MD Anderson: This is not more compelling than other evidence I've seen. I mean, like any academic, I'm very interested in how people are look-

ing at something in a different way. I think this should definitely be an academic debate.

I think we as scientists look at each other's work and say, "Oh, what method are you using? What are you doing? How'd you come to this conclusion?" But this should not directly change how we advise the public. I'm interested in it as a scientist. I read it, I found things I like about it and things I don't like about it, including things I think are missing, and things I think are thought-provoking.

But it doesn't change several decades of research that I have personally done, and that my colleagues have done, and that we have discussed, and we have viewed. We have understood the mechanisms behind how meat promotes cancer.

This study does not change the way I feel about what I would tell the public, about what they should do to reduce their risk of cancer. It does not change that.



McCullough, ACS: The relative risks that they show are actually quite compelling and supportive of current guidelines. The difference is that they present the risk difference over the lifetime of an individual of cutting back or of limiting red meat or processed meat. These risk differences for their likelihood of getting these diseases over their lifetime may seem small.

For some of them, and myself, if I were to look at those overall cancer mortality numbers, I would actually say, “Huh, well that doesn’t seem that small to me.” For rarer outcomes, absolute risk differences appear quite small. If your lifetime risk of getting gastric cancer is 14 per 1,000 people, and it would go down to 12 per 1,000 people with lowering processed meat intake. If I were presented with these statistics, I would say, “Well that’s a way to cut back on my risk.”

But the authors’ argument is that these associations are really too small to be of benefit to individuals. And they also graded the evidence using a grading system that is typically used for pharmaceutical trials. In reviewing the evidence for diet and lifestyle, we tend to use different review criteria, because it’s really difficult to do long-term trials of diet and cancer.

It’s almost impossible, for example, to study the impact of increasing red and processed meat in cancer outcomes, because of practical and ethical reasons. There has been some question as to whether these review criteria were appropriate in this setting to study meat and long-term outcomes like this, which are typically not amenable to randomized controlled trials.

As a result, they rated the quality observational studies as weak or very weak. Maybe this is getting into the weeds, but they would downgrade the evidence if there weren’t repeated measures of diet during the course of a prospective analysis. And they would downgrade if, for example, family history was not included in the model.

Some have argued that the criteria are inappropriate for studies of diet and long-term health outcomes. They graded the evidence as weak, which is why, combined with some small risk difference and combined with their examination of meat preferences, they came to the conclusion that people should continue to do what they do now.

I find their relative risk compelling. It’s informative to have the risk difference calculated. I don’t find their argument and conclusions compelling, because of the reasons I just cited, because of the criteria that they graded the prospective studies on.

I don’t agree with their recommendation. The title of their paper is, “Unprocessed Red Meat and Processed Meat Consumption, Dietary Guideline Recommendations...” It wasn’t clear to me whether they were actually posting guidelines, or if they were saying “we recommend that guidelines do this.”

Harris, UNC: When discussing the magnitude of association between red and processed meat consumption and all-cause mortality and adverse cardiovascular outcomes, the magnitude of association would not be small, it would be certain.

If you’re talking about evidence, you need to talk about certainty. If you’re talking about magnitude of effect you need to talk about how small the size. So, don’t talk about small when you’re talking about the evidence. You’re talking about certainty when you’re talking about the evidence, and you talk about small when you’re talking about magnitude. Just be sure you got that straight.

You’re trying to inform and help people understand, not only this time, but also future times, because, remember, the issue you brought up here is a pretty common issue. This comes up with physical activity, prevention of lower back pain, seat belts, screening for diabetes, screening for glaucoma, screening for hepatitis C.

Those are all issues in which we’re talking about, “Is the evidence enough to make a recommendation?” And that’s really where we are with this. Is there enough evidence here to say anything other than, “I don’t know”? The third is-

sue here has to do with what you should make a recommendation on.

The second part is the magnitude of effect. And I think, again, they’re correct in that the absolute magnitude of effect, if there is a magnitude—so, remember that if we have really lousy, lousy evidence, we can’t say what the magnitude of the effect is, because we don’t have the evidence to say anything, or provide any recommendations or guidelines.

Assuming that all of that evidence that we have—even though it’s low or very low certainty—assuming that that’s correct, then the magnitude of effect is, in absolute terms, small. Or even very small, or in a few cases, non-existent. And so, I think that’s real clear, too, from the evidence.

Are these guidelines coming from researchers and scientists that the public can trust?

Reedy, NCI: This was a self-appointed panel, and I know that we’ve heard from other reports that there is some disagreement among the authors. Not all the authors agreed with the language and the final papers.

Redberg, UCSF/JAMA: I don’t know the team, but I assume this manuscript underwent peer review just like any other manuscript would in a high-quality medical journal like *Annals*.

Daniel, MD Anderson: I don’t know them personally. They’re not the same cohort of nutritional scientists that that serve on the AICR. I don’t know enough about them to make that kind of assessment.

McCullough, ACS: Different experts can look at the same data and come up with different conclusions or recommendations.

Harris, UNC: All of us have inherent biases built into us. And so, it's never true that we're not influenced by our own prior ideas about these topics. And these people, like all of us, have prior ideas about them. And so, clearly, they're influenced by those, but there's no financial gain, as far as I can tell.

The best way to deal with that problem with prior thoughts and prior opinions is to be explicit and transparent. And I think they have done that. They're explicit about what they did and they're transparent about their methods. And so, I think that's all good. I don't think there's a lot of debate about the certainty part.

Is this the right context for a conversation about thresholds for evidence-based guidelines? If the evidence is of low certainty or very low certainty, and the effect is small or nonexistent, should the investigators be saying, "We really don't know," instead of recommending, "Maintain your intake"?

Reedy, NCI: It's really important to look at the total diet in order to provide the best dietary guidance. This concept of a healthy eating pattern, the total dietary pattern, is a guiding principle that we see in the work of the nutrition experts who are part of the dietary guidelines committee, the AICR/WCRF reports, and also among other leading global researchers. It's clear that there can't be guidelines for one aspect of the diet without considering what that means for the rest of the diet. We know these pieces are all intertwined and interconnected.

Nicastro, NHLBI: I think the Dietary Guidelines are still appropriate. Re-

member, this is one study making one conclusion. The Dietary Guidelines for Americans consider a very broad body of evidence and draw conclusions based on that data using rigorous methodology.

Redberg, UCSF/JAMA: I think it has been clearly established from multiple large-scale epidemiologic studies that there is a health benefit, a cancer benefit, cardiovascular benefit, and survival benefit associated with plant-based diet.

Daniel, MD Anderson: I want to make a couple points. One point is that the effect of diet on cancer and cardiovascular disease is cumulative. So, you asked me your first question about whether to eat a kielbasa tonight. Well, you're not going to impact your cancer risk that day, with that decision. However, again, looking back at mechanisms like DNA damage and inflammation and the impact on the microbiome, we can see that within a day, or a month. We can't see whether or not you're starting to grow cancer for some time.

Flawed or not flawed, the reality is, large epidemiologic studies are the best way to look at those long-term effects. And we take into account research from those long-term observational studies, experimental studies, and trials with the intermediate outcomes. We take that all together, and we make a general conclusion.

The other thing would be that, again, they use a different method. The way that they weighted each piece of evidence is going to result in slightly different answers than the way someone else weighted the evidence. The results are not new, just the magnitude of what they're focusing on is slightly different than what you get when you look at the whole picture. But it's not that they did something wrong, it's just they did it the way that they chose to do it.

They were focusing on the perspective of individual decision-making, not on public health recommendations. That's incredibly important to make that distinction. So, they had a different purpose going in, and so, they took a different approach. Again, in my mind, taking that approach doesn't mean that we should change the dietary recommendations for health. You know, people may not want to give up smoking. Does that mean that we should stop telling everyone to stop smoking? No.

That's an interesting thing to think about when we think about policy decisions or what challenges we're going to have in our approach to enacting those public health recommendations, but they don't change whether the evidence is there, and whether that recommendation should be made.

I've worked on studies where we've actually found fairly large effect sizes from eating red and processed meat with large prospective studies. It's individual to the cancer. In colorectal cancer, we've seen very large effect sizes. In breast and prostate cancer, we see lower effect sizes, because they're totally different cancers that develop from totally different mechanisms.

So, if you mash it all together, the low ones and the high ones, you're going to get something modest. But that doesn't mean that red and processed meat does not cause colorectal cancer. From a mechanistic standpoint, it does.

McCullough, ACS: I think we have to have a conversation about which methods they used to evaluate the evidence for lifestyle behaviors. As I mentioned, the methods they employ here really downgrade the evidence of any observational studies, and in this case, prospective cohort studies.

Currently, other major organizations that review the literature, for example, the World Cancer Research Fund and

the American Institute of Cancer Research, use different sets of guidelines.

Oftentimes, the best data that we have for evaluating lifestyle and cancer outcomes, for example, is using large prospective cohort studies.

Harris, UNC: My answer to that is that's the issue of what we call the thresholds. There are several thresholds in evidence. One threshold has to do with how much evidence you need, how sure you have to be, how certain you have to be before you make any statement, before you make any recommendation.

Let me point out that's the reason the US Preventive Services Task force has what they call an "I." They're one of the only guideline groups that have something called an "I"—insufficient evidence—that means we looked at the evidence as hard as we could. And guess what? This doesn't answer the question that we wanted to ask.

And so, therefore, what we're going to say is, "We don't know the answer." If you look at most other professional groups, the American Cancer Society and a whole bunch of others, they all say, "Well, you know, the evidence is really lousy here, but we're going to give you, basically, our opinion, our thoughts about it anyway."

In the end, you're not sure where this recommendation came from. Did it come from somebody's prior beliefs, like we talked about before? Or is this really something the evidence is real clear about? And so, I would say that, especially looking at it here, that the prior recommendations have been way too certain.

They have told us that we should not eat much red meat, processed or unprocessed, and that that's bad for our health. And they came on way too strong given the evidence. That's basically what these folks are doing. They're calling the bluff of the previous recom-

mendation statements, and they're right to do that.

Those statements were based on, at best low-certainty or very-low-certainty evidence. The problem is that then, the authors go right ahead. They make the wrong recommendation. They make the same mistake, to me, that others made before. And so their statement, I'm reading this verbatim, "the panel suggests that adults continue current, unprocessed red meat consumption." They have a weak recommendation, based on low-certainty evidence. Similarly, their panel suggested adults continue current processed meat consumption. Well, that's different from saying, "We don't know the answer."

What they could have said is, "The evidence is insufficient." They could say, "This evidence is so lousy that we can't tell you whether eating meat is bad. Certainly, there's no signal here that it's good for you, by the way. But we can't tell you whether it's bad for you or not. So, you're going to have to decide this based on other things."

Are the studies methodologically sound?

Reedy, NCI: There are a lot of concerns with different things that are going on. A key point here is that we see the authors reviewing existing literature. There's nothing new here that they're looking at, and they're observing similar results as other reviews have. They're applying a different metric to those results, and they're inferring something different from that.

Nicastro, NHLBI: They ask the question of comparing high to low intakes of red meat, and they put higher weight on randomized controlled trials. Of the 12 randomized controlled trials they have, one contributed most of the

participants. About 80% of the participants came from the Women's Health Initiative Dietary Modification Trial, and that trial did not advise participants to decrease or increase red and processed meat intake. They instead asked people to lower dietary fat intake in the intervention group, compared to the control group.

And that's true of most of the 12 intervention or clinical trials included in the analyses, as they weren't clinical trials specifically designed to address differences in meat intake. And, in fact, they state very clearly, out of the 12 studies, none of them achieved a gradient of more than a serving per week difference in red or processed meat.

So, elevating this evidence doesn't necessarily make sense in this context.

Daniel, MD Anderson: I do not want to comment on whether these individuals had made all the right decisions or not, because this is science, and we all take approaches, and we need to break paradigms, and that's part of our job.

However, the problem is, when we are acting as scientists, the public perception is that we can't come to a consensus, or we don't know anything, or we change our mind every day. And that's not the truth. The professional consensus, as you probably have noticed, has not changed.

I think everyone has the right to look at things with a different method. It doesn't mean that one is better than the other, but we shouldn't change our professional consensus on one group's attempts or one group's approach.

McCullough, ACS: The authors grade the certainty of evidence as low or very low in part because of the potential for residual confounding in observational studies. They did not consider dose-response relationships, and in their abstract consider recall bias a limitation; however, for prospective studies, recall

bias is limited, because diet is assessed before diagnosis.

It's impossible to conduct randomized trials for every diet question. Smoking, diet, physical activity, alcohol and body weight, all of these known risk factors for cancer and other outcomes are very difficult to test in a randomized controlled trial setting for reasons of cost and practicality, and in some cases ethical issues.

There are other modified grading systems that have been applied for observational studies that have been employed by both the USDA and the World Cancer Research Fund, where they consider the consistent findings across multiple cohorts, large numbers of participants, long duration of follow-up, low dropout rates and dose response relationships.

Of course, most guidelines also consider supportive biological mechanisms, and also randomized trials, when available. A lot of times in randomized trials—though it's not always practical to study cancer outcomes using a randomized trial—randomized trials of potential mediators of cancer, such as inflammation, or mediators of cardiovascular disease, such as blood lipids or blood pressure, can also be considered in making recommendations.

The authors found 12 eligible trials to look at meat intake and cancer, and cardiometabolic outcomes. The authors' own conclusions were that there were a few trials where they were able to really look at differences in red meat consumption, but the trials, for the most part, were of other dietary questions. The authors note these limitations.

For example, the only trial of cancer outcomes was the Women's Health Initiative. That was a low-fat trial. They didn't specifically have people cut back on meat. That wasn't the main objective.

Because they weren't directly looking at changes in meat in the trials, they actually did downgrade the level of the evidence. They weighted the trial data poorly as well. They said that the evidence from randomized trials was that diets lower in red meat may have little or no effect on all cause mortality, cardiovascular disease and total cancer mortality, but they had limited evidence with which to make these conclusions.

There is an inverse association for total cancer mortality in the one trial, but it's not statistically significant. Essentially they say, 'We did not see that the trial data shows an association of red and processed meats with lower risk of outcomes either.' They also acknowledged that the evidence is low to very low certainty.

It's also not clear from their summary of the trials what the original study outcomes were.

Basically, for mortality outcomes, they based it all on the Women's Health Initiative. For cancer, the evidence was rated down to very low certainty, owing to risk of bias, imprecision or serious indirectness, meaning that the study wasn't designed to study the effect of lowering meat intake.

Harris, UNC: I think they did the best they could. I mean, remember that these things are hard to measure. There's not a blood test you can do that will tell you "Is this processed or unprocessed meat?" And by the way, that's going to change from the time you're 25, until the time you're 35, until the time you're 55. And then the outcomes start happening when you're older and you've been changing and back and forth for many years.

And so, this is a really hard thing to study, and I think they did the best they could. I wouldn't fault the reviewers for the deficiencies in the literature. It

is true that there are these deficiencies in nutritional epidemiology, but that's not their fault. They're simply trying to put together all these studies that have been done, faulty as they are, and say, can we make any sense of this?

Validation has to do with replication, but that's what systematic reviews are about. See, these folks didn't actually follow a cohort of people. Their subjects are the studies themselves. So, they are sampling from the universe of studies, not from the universe of people. The studies have sampled from the universe of people.

The question you should be asking then, for replication is, "Did they sample fairly from the universe of studies?" The issue of replication would be, if they had found that one study found one thing and another study found something wildly different, and the third study found something even different again, then you would say it's not replicable. Either they're not studying the same thing or whatever the first study got is not being replicated in the other study.

What these guys are doing is looking at that issue of replication. Did all these studies agree or disagree? I'm sort of making a generalization here, but they're finding that there's a lot of agreement among these studies. It's just that all of them are flawed in certain ways and so, that's why the certainty is low.

The evidence is flawed, because of all the problems with nutritional epidemiology that we just talked about. It has to be over time, it has to measure processed versus unprocessed meat, what people are eating now versus what they were eating 30 years ago, and then, we don't know what they replaced the meats with if they stopped eating meat. There are all these problems with this kind of study.

When evaluating food and dietary patterns, does it make sense for the investigators to assign more weight to results from randomized trials over observational studies?

Nicastro, NHLBI: While randomized controlled trials are the gold standard, these weren't randomized controlled trials designed to answer the questions that the authors are asking.

They included 23 cohort studies, which do not involve randomization. In general, we do place more weight on randomized controlled trials, but again, the randomized controlled trials identified for this analysis did not all seek to answer the question about lowering intake of red or processed meat.

Daniel, MD Anderson: It's true that randomized clinical trials are the gold standard. However, the kind of trial that people want is impossible. We cannot get individuals to leave everything in their diets the same and just change meat intake and follow them for 10 years to see who gets cancer.

The other problem I have whenever this stuff comes out is this reductionist approach and focusing on one food. We do not make dietary recommendations based on one food. If you read the dietary recommendations, there is substitution, there are multiple components. It's an entire dietary pattern.

Redberg, UCSF/JAMA: I'm very much a believer in evidence-based medicine and in high quality science. But I don't think that we should be applying those same standards when we're talking about what people eat and food research. For that reason, I don't think that we need to weigh randomized trials more highly when we are talking about food research.

I think perhaps that's why this group of authors had a different interpretation, because for some reason, they decided that nutrition research and food recommendation should be held to the same standard that we would hold drug or device studies. I just don't think that is a reasonable presumption. I don't subscribe to it.

McCullough, ACS: It would be very difficult to conduct randomized trials of red and processed meat because of the long duration, for practical reasons, and for ethical reasons. In this case, observational studies were given a weak rating, or low certainty of evidence because of the fact that they're observational.

We have other criteria for examining the observational evidence, including consistency of findings across studies and evidence of dose response relationships. The other organizations that typically review this type of data have been considering these criteria.

I mean, it would be great if we could do randomized controlled trials on all things that we believe influence health outcomes, but that's not feasible and trials have their own sets of limitations.

I don't think that these studies necessarily change the way we interpret the data. The absolute risk difference is small. We've known that for some outcomes and some exposures, but for some individuals it will have more of an impact.

When you look at the population-wide associations, they can have significant impact.

As far as physicians are concerned, it's important to inform patients of existing guidelines. I don't think that this latest set of findings should change what the guidelines are.

I don't think it changes our recommendations, and also I think physicians can have that discussion with patients

that these are the recommendations. The absolute risk for some outcomes is small, but it's important to consider a patient's current diet and clinical risk profile.

Harris, UNC: Now remember, what all the studies are looking at—the one randomized trial that they looked at with Women's Health Initiative, all the observational data would say that what they're looking at are people's reports or, in some cases, better measurements, like health diaries and such about what they've eaten over time.

But people's diets, (a) don't stay the same all the time, (b) they don't report them exactly correctly as we would like them to and (c) if they don't eat meat, we're not really clear about what they do eat in place of the meat. And so, there are time problems and replacement problems and measurement problems and all those. And so, that's the evidence that they're looking at. Flawed as it is with all these problems attached to it, that's just the nature of the beast with nutritional epidemiology, as others have pointed out. So, it's a problem.

But at any rate, if we think that what they're looking at is important and really gets at the question we have—which I'm not sure it does—and the absolute effect is smaller, very small, or occasionally nonexistent, those are the first two parts of this.

The one randomized trial, the Women's Health Initiative, that they talk about—they looked for all other randomized trials, and it's pretty hard to do a randomized trial, as you might imagine, you'd have to randomize people to those who eat a whole lot of meat and those who don't eat much meat. And people are not very good at following what they were told to do anyway. Then, you have to do it over a long time. And this study really only had people changing their habits for six months to a year, or something like that.

So, you might imagine all the problems with observational studies, but there are also problems with randomized trials, because one, people don't adhere to what you asked them to do. Number two, you have to do it for a long time, which this study did not. You have to have a whole lot of people, and you have to follow them for a long time.

With nutritional epidemiology, not only are observational studies a problem, randomized trials are a problem, too. The fact that the Women's Health Initiative didn't find much after just having people change their diet for a year or so, it wouldn't be very surprising to many of us.

I mean, it's not a very strong intervention, which would be quite different from certain groups of people who eat very little meat for their entire lives. That would be a very different kind of intervention. But of course, they're not randomly assigned.

While no one is suggesting increasing consumption, should these new recommendations supersede or inform previous guidelines, which suggest limiting or reducing consumption?

Reedy, NCI: These so-called guidelines that they report shouldn't change our current recommendations on diet and disease risk. The recommendations that we have in the literature that underpin guidelines that currently exist are based on clear evidence looking at including things like randomized clinical trials with cardiovascular disease and risk factors related to cardiovascular disease.

We also have longer-term observational studies looking at cardiovascular disease and cancer, Type 2 diabetes and mortality. Our guidelines here remain the same regarding dietary patterns

that are high in plant-based foods like fruits, vegetables, whole grains, and lean protein foods, and low in added sugars, saturated fats, sodium, sugar-sweetened beverages, and red and processed meats.

Nicastro, NHLBI: The Dietary Guidelines for Americans still stand.

Redberg, UCSF/JAMA: Oh, absolutely not. No, I would not change the guidelines based on these studies. Obviously, this wasn't any new data. It's a different way of looking at the data and saying that food recommendations should be based on randomized studies. I don't subscribe to that premise.

I have read many, many large epidemiologic studies and meta-analyses over the last 25 years that also are consistent in finding that people that eat less red meat and less processed meat live longer and have less cancer and heart disease. It would be hard to see how this different interpretation of the quality of evidence required for future research could be used to change the guidelines.

I don't think there is any kind of widespread consensus that we should be doing randomized trials for food research. There's widespread consensus that epidemiologic studies work for food, and to some extent for physical activity as well, which is another lifestyle. For smoking, I think we've all accepted cigarettes are a cause for cancer, and we didn't have randomized studies to prove that.

Daniel, MD Anderson: I don't think the evidence about red and processed meat and cancer is insufficient. I think that there is a long history of research in this area that even is outside of what we discussed.

Meat is just one line of the dietary recommendations, but it gets a lot of attention. So, you can't completely change your risk profile by just moving meat up and down without changing other components of your diet. And I think

something in the paper that was sort of buried was the dietary patterns that are traditionally lower in red and processed meats, like the Mediterranean diet. The Mediterranean diet has been associated—in several studies and trials—with lower risk of cancer and cardiovascular disease.

We need to focus on what the dietary recommendations actually intend to do. They want you to eat less red and processed meats and instead, they want you to choose fish, lean protein sources and vegetable protein sources like beans and legumes. If you do all that in its entirety, you will lower your cancer risk. If you fixate on whether you can have a steak tonight or not, you're not going to get very far.

Those recommendations have been fairly stable for the past 40 years, and there's a reason why. The evidence does not fluctuate that much. Like I said, we have to take this as one set of publications dropping into a giant bucket of other publications. And when you drop it into the whole mass of evidence that's there, usually that is not as dramatic as you think it is.

Our job is to do our best to cure and prevent cancer. And that's not the purpose of this review.

McCullough, ACS: No, I don't think these findings should supersede existing recommendations that have been vetted by panels of experts in nutrition and cancer.

As far as what physicians should say, physicians should say that public health recommendations are to limit intake of red meat and processed meat. You don't have to eliminate it. We don't have to eliminate red meat, but cut back on intake levels.

The American Cancer Society doesn't have a specific cut point for red meat or unprocessed red meat, because the evidence shows a linear positive asso-

ciation with more meat intake. So, it's really saying that the more you cut back, the better. Red meat has some redeeming value. It has B12, zinc, iron and high quality protein.

We recommend that people who do eat red meat choose lean cuts and limit their consumption. The World Cancer



This wasn't any new data. It's a different way of looking at the data and saying that food recommendations should be based on randomized studies. I don't subscribe to that premise.



— Rita Redberg

Research Fund and the American Institute for Cancer Research recommend unprocessed red meat no more than three times per week. And that's in the context of the whole day, including breakfast, lunch, or dinner. And then limiting processed meat to eat it only occasionally, if at all, because processed meat was classified as carcinogenic to humans according to the International Agency for Research on Cancer of the World Health Organization.

And the panel of 22 international experts considered the evidence from observational studies as well as mechanistic data from in vitro, animal and human studies. They also classified red meat as "probably carcinogenic to humans." Both classifications were based on evidence for colorectal cancer.

For that reason and the totality of the evidence, largely from prospective cohort studies, we recommend people limit red meat and processed meat intake. My opinion is that if the physician is talking with the patient, they could let them know that these are public health recommendations based on evidence from large studies and mechanisms that have been reviewed by international panels and large health organizations.

I think the authors are to be commended for their very thorough systematic literature review and their contribution of summarizing the individual risk differences. I think that's informative. However, what it really comes down to is the grading system applied to lifestyle factors. If we consider that all observational studies will be ranked as insufficient, or most would be, then we would not be telling people to do anything different.

That's may be a bit of a broad statement, but I think that would be irresponsible, because we know a lot from observational studies and from these very careful comprehensive reviews of the literature that have arrived at these guidelines. We could really do a disservice to the public if we ignore all of this evidence.

Harris, UNC: To me, they made the same mistake that they're calling others out for having made. That's an error. When I was on the USPSTF, the way I would have voted if this had come up for us, I would have said, "This is insufficient evidence. It's a good question, but I don't know the answer. You should make your decision based on other things."

I think it might've been controversial either way. This is just a tough issue. They're calling out some people for past recommendations.

They're really not saying this directly, but in a way they're saying, "You guys are way too certain about what you told the public." By the way, that's the kind

of thing that makes the public deeply skeptical about whatever scientists say, when scientists come on to seem to know more than they really know.

In this current situation, even if the recommendation had been something like a Task Force "I," if they said, "We can't tell you, you should make your decision based on other factors," I think even then, they would've gotten blow-back.

It might not have been quite as bad, but I still think that people who had previously made strong recommendations on cutting back on meat would still have been incensed. I don't know that there's any way around that, just because they're deeply committed to what they have already said in the past. But, according to the evidence, it's just not there.

What would you tell your patients? What is your message to the public?

Reedy, NCI: It's really challenging to identify all the different strategies that are needed to combat these kinds of sensational headlines and so-called guidelines like this that aren't based on scientific evidence.

In a clinical setting, there are many different things to consider for a patient, and what their particular context and issues are. Similarly, for the public and for population health, guidance is grounded in the broader food environment, and how we can best support people to make healthy choices.

The recent study is of concern, because the public could interpret this as an actual new guideline. In reading these papers, it's important to look across that totality of evidence and understand how current evidence-based guidelines are developed.

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The recent study is of concern, because the public could interpret this as an actual new guideline. In reading these papers, it's important to look across that totality of evidence and understand how current evidence-based guidelines are developed.

—Jill Reedy

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NICASTRO, NHLBI: The Dietary Guidelines for Americans don't limit any one protein source, but they do recommend a healthier eating pattern with more lean meats and limited red and processed meats. And that is still the recommendation that we should be putting out to the public.

REDBERG, UCSF/JAMA: I will continue to recommend a Mediterranean-style diet. I like what Michael Pollan said, "Eat food. Not too much. Mostly plants." And get regular exercise.

The other thing, and I think the authors said, "Well, it's not our problem," but besides the benefit directly from eating a diet with less meat—and it doesn't have to be no meat, but certainly a lot less meat—there's the effect on the environment.

There is a huge component of cows and methane production, and the inefficient protein that you get from eating meat that contributes to climate change. I think what I read, they also said climate change isn't their problem, but climate change is all of our problems. I don't agree with saying that that is not another reason that we should all be eating less meat. We have a very serious crisis of global warming, and meat consumption is contributing to it significantly.

We have to be careful to be as clear and consistent as we can, and I think, with diet, we certainly have a lot of good reasons to be very clear and very consistent that limiting the consumption of red and processed meat is really good for your health.

DANIEL, MD ANDERSON: Continue to follow the dietary recommendations in their entirety. Take a look at them in their entirety, which is to eat more plant based foods, fiber rich plant foods, fruits, vegetables, legumes. If you're going to consume grains, consume whole grains. If you're going to consume meat,

consume fish, consume lean proteins and consume vegetable-based proteins, and limit added sugars.

Overall, eat a variety of foods, but not too much. That has not changed just because a paper has come out on this. And, like I said, the evidence is actually strongest for processed meat that is red. There are different levels; a hamburger may not be the same as a piece of bacon in terms of how it impacts cancer mechanisms.



But we don't get into that level of detail with public health recommendations. To make an analogy, we know that when we're treating cancer, we usually start with the standard-of-care therapy. They don't work for everyone; does that mean that we just throw them out the door and do something else?

No, we have to have a process to get to that and this paper has not changed that process. It becomes a part of that process, but that process is not being thrown out the window.

MCCULLOUGH, ACS: This is a comprehensive systematic review of the evidence on meat consumption, whether reducing meat intake will influence cancer outcomes and other causes of mortality, and the authors actually find very

similar associations that have been reported by others. So, in that sense, it's confirmatory. The difference is in the interpretation of the data for individuals versus population benefits.

The American Cancer Society continues to recommend that people limit their consumption of unprocessed red meat, and especially processed meat, based on the totality of the existing evidence and conclusions by the World Health Organization that processed meats are carcinogenic and unprocessed red meat is considered a probable carcinogen.

The preponderance of the evidence is also reviewed using systematic literature reviews by the World Cancer Research Fund/American Institute for Cancer Research. The current set of papers, again, really reinforce the risks that we've seen. The study uses different criteria for weighting the evidence, and they come to different conclusions based on their weighting of the evidence, and based on their consideration of people's preferences for meat.

We used the authors' estimates to calculate that by lowering processed meat intake by three servings per week, the number of lives saved from cancer death would be 8,000 per one million people.

Harris, UNC: I would say that a group of investigators—by the way, it's not the journal that made the recommendations—has done a superb job of bringing together the literature on meat consumption and health. And what they have found is that the evidence of association between meat consumption and health has low or very low certainty. Even if we take whatever evidence we have as being sufficient, the magnitude of any effect in absolute terms is small or even very small.

Because of the literature being as difficult as it is, we cannot answer the question as to whether reducing meat consumption would improve health.

People should make their decision on meat consumption on other grounds.

There are really clear ethical and environmental reasons for cutting back on red meat. As environmental studies have shown recently we should be planting more trees and eating less red meat if we want to protect the planet.

Let me just say that we talked about this one threshold—when you're doing reviews of evidence, that one threshold is, "How sure do you have to be? How certain do you have to be before you can make a recommendation?"

I'm suggesting that the threshold is higher than these folks did. So, these folks said, "This threshold is high enough for us to go ahead and say, 'Keep doing what you're doing.' I'm suggesting that the best threshold would be higher than that, and we should say, in all honesty, to the public that this evidence is insufficient, so we can't make a recommendation.

Let's say we had enormous randomized trials, and they were really well conducted over many, many years. It's impossible, but let's say that we had those. The second threshold would be, "How big does the magnitude of benefit need to be before we make a positive recommendation?" And that comes up a lot also in evidence reviews.

The question about how big the effect is, is kind of a separate issue. Everything here has to do with the magnitude, with the certainty issue, the threshold, and how good is the evidence. The evidence here is really lousy.

We've written seven or eight different articles about evidence like this at the USPSTF, and we try to keep those two thresholds separate so that people can understand better. But here, the big issue is the threshold of certainty, and I don't think the evidence has met it. And the authors seem to think that it did meet it.

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We used the authors' estimates to calculate that by lowering processed meat intake by three servings per week, the number of lives saved from cancer death would be 8,000 per one million people.

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– Marji McCullough

IN BRIEF



Barry Kramer receives Friendship Award from the People's Republic of China



Barry Kramer, former director of the NCI Division of Cancer Prevention, has received the People's Republic of China Friendship Award, the highest honor given to non-citizens.

Kramer received the award on Sept. 30 for his work with the National Cancer Center of China, part of the Cancer Institute of the Chinese Academy of

Medical Sciences. This year, he was one of 14 Americans to receive the award, and one of two health care professionals out of 100 awardees from 31 countries. The award has been given annually since 1991.

Kramer was nominated by the National Cancer Center for designing cancer screening studies and his leadership in translating NCI's Physician Data Query into Chinese. The PDQ has been translated into Spanish, Japanese and Arabic.

From NCI, Margaret Beckwith, acting branch chief for the PDQ Cancer Information Branch; Martina Vogel Taylor; Ping Hu; Philip Prorok; Richard Fagerstrom; and Paul Pinsky, all in the Division of Cancer Prevention, were central to the collaboration with the People's Republic of China. From China, He Jie, director of National Cancer Center of China, and Dai Min, also of NCC, worked with the NCI team.

Kramer retired from NCI in 2019 (*The Cancer Letter*, [Nov. 2, 2018](#)). He is a consultant in the NCI Division of Cancer Control and Population Sciences and an honorary professor at the National Cancer Center.

Moffitt forms immunotherapy CRO

Moffitt Cancer Center has formed a contract research organization to accelerate the institution's immunotherapy research.

The subsidiary, which was announced Oct. 3, is intended to provide a one-stop-shop for pharmaceutical and biotech companies to accelerate their immuno-oncology and cell therapy research through collaborative clinical trial support and administration.

"There are currently no other immunotherapy clinical research organizations in the United States. We can provide

a much needed service that will bring new immunotherapies to patients more quickly," Moffitt's Center Director and Executive Vice President at Moffitt, Thomas Sellers, said in a statement.

Moffitt is seeking investment and partnerships to support the wholly-owned, for-profit subsidiary. The cancer center will appoint a board of directors to oversee operations. The CRO is expected to be fully operational in nine to 12 months.

The cancer center has enrolled more than 3,000 patients in immuno-oncology studies over the past five years. The center was involved in clinical trials that led to the approval of CAR T-cell therapy.

The new CRO will offer services that include preclinical study, manufacturing, clinical trial design and oversight, data management and regulatory assistance. The goal is to take a company's drug or medical device from initial discovery to clinical testing and FDA approval.

"We have a facility certified in Good Manufacturing Practice, a system for ensuring that products are consistently produced and controlled according to quality standards, that is producing these therapies and will establish a network of partners to facilitate multi-center clinical trials," Brian Springer, Moffitt's vice president and associate center director of research administration, said in a statement.

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Adding targeted therapy drug to hormone therapy helps aggressive breast cancer patients live longer

Adding Kisqali (ribociclib) to standard hormone therapy significantly extended overall survival for postmenopausal patients with HR+/HER- advanced breast cancer in the phase III MONALEESA-3 trial.

The findings also show the combination treatment is beneficial with the longest time of recurrence today in first-line therapy, and should become a first-line option in postmenopausal women with HR+/HER2- advanced breast cancer.

Dennis Slamon, chair of hematology/oncology and director of Clinical/Translational Research at the UCLA Jonsson Comprehensive Cancer Center, presented the results Sept. 29 at the 2019

European Society for Medical Oncology Congress in Barcelona.

“Many people argue that the first type of treatment women with this type of metastatic cancer should receive is some other form of hormonal therapy and then wait to see if they respond to that treatment,” Slamon said in a statement. “But we found there’s a significant difference when you use the combination of ribociclib with hormone therapy as the first line of therapy. There is absolutely no reason to wait to give women this treatment. This should be the new standard.”

This is the second phase III trial where Kisqali combination therapy met the secondary endpoint of overall survival at the pre-planned interim analysis. MONALEESA-3 evaluated efficacy and safety of Kisqali plus fulvestrant in postmenopausal women with hormone-receptor positive, human epidermal growth factor receptor-2 negative (HR+/HER2-) advanced or metastatic breast cancer.

“Increasing overall survival is the hardest endpoint to move,” Slamon said. “We’re also seeing that the time of progression-free survival is the longest yet reported for any of the drugs in this class. And even when patients are off the drug, the effect seems to be long-lasting in terms of the benefit. It’s important because this means we are helping women live longer and have a better quality of life.”

The results on data previously reported by Slamon and colleagues helped lead to FDA’s approval of ribociclib. There are three CDK 4/6 inhibitors that have been approved by FDA for combination treatment with standard hormone therapies.

The double-blind clinical trial involved 726 postmenopausal women who had advanced hormone-receptor positive/HER2- breast cancer. The trial included women who had not received prior endocrine therapy as well as patients who were in the first-line or second-line setting.

The results demonstrated a statistically significant improvement in survival with a 28% reduction in risk of death. At 42 months, the estimated rates of survival were 58% for the drug combination treatment and 46% for women who were treated with the hormone therapy alone.

The median progression-free survival with ribociclib plus fulvestrant in the first-line setting is the longest reported in a phase III trial in hormone-receptor positive/HER2- breast cancer at a median of 33.6 months, compared to 19.2 months for those in the hormone therapy only group.

Kisqali in combination with fulvestrant met its secondary endpoint of overall survival, demonstrating a statistically significant improvement in survival with a 28% reduction in risk of death (median OS not reached vs. 40.0 months; HR=0.724; 95% CI: 0.568-0.924; p=0.00455).

The significant extension in survival met the early efficacy stopping criteria at a prespecified interim analysis. At 42 months, estimated rates of survival were 58% for Kisqali combination treatment and 46% for fulvestrant alone. Results in the first-line and second-line subgroups, including in patients who relapsed within 12 months of adjuvant treatment, were consistent with the overall MONALEESA-3 patient population.

Median first-line PFS was also reached at this analysis and demonstrated that Kisqali in combination with fulvestrant has a median PFS of 33.6 months compared to 19.2 months in the placebo arm (HR=0.546; 95% CI: 0.415-0.718). Additionally, the need for chemotherapy was delayed in all patients who were prescribed Kisqali plus fulvestrant (HR=0.696; 95% CI: 0.551-0.879).

Other investigators are Patrick Neven, Stephen Chia, Peter Fasching, Michelino De Laurentiis, Seock-Ah Im, Katarina Petrakova, Giulia Val Bianchi, Francisco Esteva, Miguel Martín, Arnd Nusch, Gabe Sonke, Luis De la Cruz-Merino, J. Thaddeus Beck, Xavier Pivot, Manu Sondhi, Yingbo Wang, Arunava Chakravartty, Karen Rodriguez-Lorenc, Guy Jerusalem.

The team is now evaluating these drugs in women with early-stage breast cancer in an international clinical trial called NATALEE.

The study was sponsored by Novartis, which developed ribociclib at the Novartis Institutes for BioMedical Research under a research collaboration with Astex Pharmaceuticals.

Opdivo + Yervoy demonstrate durable long-term survival benefits in advanced melanoma

The phase III CheckMate -067 trial continued to demonstrate improved overall survival with the first-line combination of Opdivo (nivolumab) plus Yervoy (ipilimumab), versus Yervoy alone, in patients with advanced metastatic melanoma.

Bristol-Myers Squibb sponsored the study.

With a minimum follow-up of 60 months, five-year overall survival rates were 52% for the Opdivo plus Yervoy

combination, 44% for Opdivo alone, and 26% for Yervoy alone. Data from CheckMate -067 was presented at ESMO Sept. 28 and were simultaneously published in *The New England Journal of Medicine*.

The safety profile for Opdivo plus Yervoy was consistent with prior findings, with no new safety signals and no additional treatment-related deaths. At this five-year analysis, treatment-related adverse events were consistent with those previously reported and occurred in 300 (96%) patients in the combination group, 271 (87%) patients in the Opdivo group, and 268 (86%) patients in the Yervoy group. Grade 3/4 adverse events occurred in 186 (59%), 73 (23%), and 86 (28%) patients, respectively.

The percentage of patients experiencing an objective response remained stable at 58% for Opdivo plus Yervoy, 45% for Opdivo alone, and 19% for Yervoy, while the percentage of patients experiencing a complete response continued to increase, with complete response rates at five years of 22% for Opdivo plus Yervoy, 19% for Opdivo alone, and 6% for Yervoy alone. In addition, the proportion of patients alive and treatment-free was 74% in the Opdivo plus Yervoy group and 58% and 45% for Opdivo alone and Yervoy alone, respectively.

Among patients with BRAF-mutant or wild-type tumors, the rate of overall survival at five years was 60% and 48%, respectively, in patients who received Opdivo plus Yervoy; 46% and 43% for Opdivo alone; and 30% and 25% for Yervoy alone. Health-related quality of life continued to be maintained during or following treatment with Opdivo alone or the combination of Opdivo plus Yervoy.

“Now, with over half of patients treated with the nivolumab plus ipilimumab combination surviving to five years, and 74% of surviving patients remaining treatment-free, we have set a new and encouraging precedent,” CheckMate -067 lead investigator and Consultant

Medical Oncologist at The Royal Marsden NHS Foundation Trust, James Larkin, said in a statement.

“The sustained long-term efficacy seen in the five-year CheckMate -067 data demonstrates the importance of dual Immuno-Oncology therapy,” development lead of Melanoma and Genitourinary Cancers at Bristol-Myers Squibb, Arvin Yang, said in a statement.

CheckMate -067 is a phase III, double-blind, randomized trial that evaluated the combination of Opdivo plus Yervoy or Opdivo monotherapy versus Yervoy monotherapy in 945 patients with previously untreated advanced melanoma. Patients in the combination group (n=314) received Opdivo 1 mg/kg plus Yervoy 3 mg/kg (Q3W) for four doses followed by Opdivo 3 mg/kg every two weeks (Q2W). Patients in the Opdivo monotherapy group (n=316) received Opdivo 3 mg/kg Q2W plus placebo. Patients in the Yervoy monotherapy group (n=315) received Yervoy 3 mg/kg every three weeks for four doses plus placebo. Patients were treated until progression or unacceptable toxic effects. Overall survival and progression-free survival were co-primary endpoints of the trial. Secondary endpoints included objective response rates, efficacy by tumor PD-L1 expression level and safety.

Data show improved OS with Jevtana over second AR-targeted agent in metastatic castration-resistant prostate cancer

Jevtana (cabazitaxel) demonstrated improved survival over second androgen receptor-targeted agent in patients with metastatic castration-resistant prostate cancer. The data were published Sept. 30 in *The New England Journal of Medicine*.

Patients with metastatic castration-resistant prostate cancer previously treated with docetaxel and who progressed within 12 months on an androgen receptor (AR)-targeted agent (abiraterone or enzalutamide) experienced significantly longer radiographic progression free survival with Jevtana plus prednisone compared with abiraterone plus prednisone or enzalutamide.

Overall survival with Jevtana was also significantly longer. These findings from the CARD study were presented Sept. 30 at ESMO.

“In this study, treatment with Jevtana significantly improved radiographic progression free survival and overall survival compared with enzalutamide or abiraterone,” lead investigator on the CARD study, Ronald de Wit, of Erasmus MC University Hospital, Rotterdam, The Netherlands, said in a statement. “These results are exciting as they have the potential to impact treatment guidelines for metastatic prostate cancer and current clinical practice.”

CARD is a randomized, open-label, treatment sequencing clinical study involving 62 sites across 13 European countries, enrolling 255 patients (median aged 70 years, 31% aged over 75 years) with mCRPC who were previously treated with docetaxel and who progressed within 12 months on an AR-targeted agent, in any order. These patients were randomized 1:1 to Jevtana (25 mg/m² intravenously every three weeks, daily prednisone, and granulocyte colony-stimulating factor) versus abiraterone (1,000 mg plus prednisone, daily) or enzalutamide (160 mg daily; patients received abiraterone if they were previously treated with enzalutamide, or enzalutamide if they were previously treated with abiraterone).

The study’s primary endpoint was rPFS, which more than doubled with Jevtana treatment (N=129) compared to abiraterone or enzalutamide (N=126; median 8.0 vs 3.7 months; HR=0.54; 95% CI,

0.40–0.73; p<0.0001). Patients treated with Jevtana experienced an improvement in rPFS in all pre-specified subgroups, irrespective of the timing of the previous alternative AR-targeted agent, before or after docetaxel. Jevtana also significantly improved a key secondary endpoint, OS (median 13.6 vs 11.0 months; HR=0.64; 95% CI, 0.46–0.89; p=0.0078), reducing the risk of death from any cause by 36% compared with abiraterone or enzalutamide.

Other key secondary endpoints all favored Jevtana: progression free survival (median 4.4 vs 2.7 months; p<0.0001); confirmed prostate specific antigen (35.7% vs 13.5%; p=0.0002) and tumor responses (36.5% vs 11.5%; p=0.004). Pain response (45.0% vs 19.3%; p<0.0001) and time to symptomatic skeletal events (not reached vs 16.7 months; p=0.0499) were also significantly improved with Jevtana treatment.

TAILORx: New data on cohort with recurrence score 26-100 shows high cancer-free rate at five years

Estimated rate of freedom from recurrence of breast cancer at a distant site was 93% at five years, an outcome much better than expected with endocrine therapy alone, data from the TAILORx trial show.

TAILORx is the largest ever breast cancer treatment trial. The data reveal clinical outcomes with chemotherapy and includes a subset of 1,389 women with a high recurrence score of 26-100. The data, which were similar to outcomes in the B20 trial (Paik et al, *JCO*, 2006), were published in *JAMA Oncology* Sept. 30 and presented at ESMO.

The finding adds to the limited data on outcomes of patients with a high RS of 26-100, treated with taxane and/or anthracycline-containing chemothera-

py regimens plus hormone therapy. It adds to the evidence base supporting the use of the Recurrence Score, a 21-tumor gene expression assay, to guide the use of adjuvant chemotherapy in early breast cancer.

TAILORx was designed and conducted by the ECOG-ACRIN Cancer Research Group with primary funding from the NCI.

“The initial results of TAILORx gave clinicians high-quality data to inform personalized treatment recommendations for women,” lead author, associate director for clinical research at the Albert Einstein Cancer Center and Montefiore Health System, and vice chair of the ECOG-ACRIN Cancer Research Group, Joseph A. Sparano, said in a statement.

“This new analysis provides the largest data set on outcomes in patients with early breast cancer and high recurrence score results. It confirms the importance of using the test to identify the minority of patients who will receive a significant benefit from adding adjuvant chemotherapy to endocrine therapy,” Sparano said.

Between 2006 and 2010, the TAILORx trial enrolled 10,273 women with hormone-sensitive, HER2-negative, axillary node-negative breast cancer at 1,182 sites in the United States, Australia, Canada, Ireland, New Zealand and Peru. Patients’ tumors were analyzed using the 21-tumor gene expression test and assigned a risk score (on a scale of 0-100) for cancer recurrence.

This analysis pertains to patients enrolled in TAILORx who had a score in the high-risk range (26 and above). These women were assigned to receive chemotherapy and hormone therapy following surgery. High-risk women were given the option to voluntarily join a prospective registry. Sufficient baseline and follow up information was available on 80% of these women (1,389 of 1,737) for inclusion in this analysis. There was

a high adherence to chemotherapy assignment (94%).

Physicians were able to select one of several commonly used chemotherapy regimens. The majority of the patients (84%) received taxane and/or anthracycline-containing chemotherapy regimens. The most common regimens were docetaxel/cyclophosphamide (42%), anthracycline without taxane (24%), and anthracycline and taxane (18%). No chemotherapy was administered in 6% (non-adherence) and the regimen containing cyclophosphamide, methotrexate and 5-fluoruracil (CMF) was administered in 4%.

Clinical outcomes in TAILORx with chemotherapy and a high RS of 26-100 ranged by type of chemotherapy. Distant recurrence-free interval rates ranged from 92-96% at five years in patients treated with taxane and/or anthracycline therapy. The regimen containing cyclophosphamide, methotrexate and 5-fluoruracil had a DRFI rate of 89%.

The expected rates in TAILORx were based on the treatment effect of chemotherapy observed in B20: 79% at five years and 65% at nine years.

The genomic assay used in the trial was the Oncotype DX Breast Recurrence Score test from Genomic Health Inc.

Verzenio significantly extends life in HR+, HER2- advanced breast cancer patients

Verzenio (abemaciclib) in combination with fulvestrant significantly extended life by a median of 9.4 months in patients with hormone receptor-positive, human epidermal growth factor receptor 2-negative advanced or metastatic breast cancer previously treated with endocrine therapy.

Lives were extended by a median of 46.7 months vs. median of 37.3 months with placebo plus fulvestrant; HR: 0.757; 95% CI: 0.606, 0.945; P = 0.0137. Eli Lilly and Company sponsors Verzenio.

Results from the phase III MONARCH 2 clinical trial, which included both pre- and postmenopausal women, were consistent across subgroups. Researchers presented the results, simultaneously published in JAMA Oncology, Sept. 29 at ESMO.

In patients previously treated with endocrine therapy whose cancer quickly returned or spread to other parts of the body, or primary endocrine resistance, the results were consistent with the intent-to-treat population (HR: 0.686; 95% CI: 0.451, 1.043). Similar results were observed in women whose cancer spread to their organs, such as liver or lungs (also known as visceral disease; HR: 0.675; 95% CI: 0.511, 0.891).

Both of these analyses were pre-defined and results are consistent with ITT results from the MONARCH 2 study that had previously demonstrated a statistically significant improvement in the primary endpoint of progression-free survival, with overall survival as a secondary endpoint.

In addition to extending life, an exploratory analysis of these data has shown Verzenio in combination with fulvestrant delayed time to chemotherapy, with a median time to chemotherapy of 50.2 months versus 22.1 months in the placebo arm (HR: 0.625; 95% CI: 0.501, 0.779). In this exploratory analysis, patients who died before receiving chemotherapy were included up until the date of death. This finding may be an important treatment consideration in advanced breast cancer as physicians aim to postpone the use of chemotherapy for as long as possible.

“While CDK4 and 6 inhibitors have changed the way oncologists treat HR+, HER2- advanced breast cancer in the

past few years, we are just beginning to understand which of these therapies meet the enormously important goal of significantly extending life in patients with advanced breast cancer,” Professor of medicine and breast oncology in the division of hematology/oncology at the University of Vermont Cancer Center, and MONARCH 2 study investigator Peter A. Kaufman, said in a statement.

“These important new findings from MONARCH 2 demonstrate further the benefits of Verzenio, and arm oncologists with additional information as they aim to optimize treatment for patients, including those whose cancer progressed following endocrine therapy,” Kaufman said in a statement.

The safety profile was consistent with primary analysis of MONARCH 2. No new safety signals were observed with long term follow-up (median of 47.7 months). At the time of analysis, 17% of patients in the Verzenio arm continued treatment versus 4% in the placebo arm.

These positive results demonstrated that Verzenio plus fulvestrant reached statistical significance at a pre-planned interim analysis. Lilly will continue to monitor patients enrolled in the trial. Any additional analyses will be considered post-hoc.

Lilly said it plans to submit overall survival data to global regulatory authorities. Verzenio in combination with fulvestrant is approved in more than 50 countries worldwide.

Additional data for investigational use of Verzenio presented at ESMO include positive results from the monarcHER trial, the first randomized clinical trial of a CDK4 & 6 inhibitor in combination with endocrine therapy versus standard-of-care chemotherapy for HR+, HER2+ patients, and positive results from MONARCH plus, the first trial of a CDK4 & 6 inhibitor in a predominantly Chinese population of women with HR+, HER2- advanced breast cancer.

Prospective trial uses blood-based NGS to identify those for treatment using Alecensa

The efficacy of Alecensa (alectinib) in patients with anaplastic lymphoma kinase-positive non-small cell lung cancer, who were identified using liquid biopsy in the phase II/III BFAST study, is consistent with efficacy in those identified by tissue analysis in the phase III ALEX study.

Genentech, a member of the Roche Group, sponsors the BFAST trial. The BFAST trial was the first prospective study to use only blood-based next generation sequencing to detect specific fusions with the aim of selecting treatment for people with NSCLC, without the need for tissue biopsy. The positive results came from a single-arm cohort.

Results from the ALK cohort were presented at ESMO Sept. 30.

“Obtaining tumor tissue for biomarker testing can be a challenge in many people with cancer and, as a result, some may not receive optimal treatment for their disease,” Sandra Horning, Chief Medical Officer and head of Global Product Development at Roche/Genentech, said in a statement. “BFAST is the first trial to show that by using a blood-based next-generation diagnostic, it is possible to identify the ALK mutation in people with non-small cell lung cancer using a blood draw alone, which means that more people could potentially benefit from Alecensa.”

Foundation Medicine partnered with Roche/Genentech on the study.

“Validated and comprehensive liquid biopsy tests are critical to help physicians find the best possible treatment approach for patients with advanced cancer and for whom tissue testing

isn't feasible,” Chief Medical Officer of Foundation Medicine, Brian Alexander, said in a statement. “Identifying ALK fusions can be particularly challenging and these data demonstrate that FoundationOne Liquid can accurately predict which patients can respond to therapy.”

The BFAST study used FoundationOne Liquid, Foundation Medicine's liquid biopsy test, which detects the four main classes of genomic alterations, microsatellite instability and select fusions including ALK in circulating tumor DNA from a blood draw.

These data demonstrate that the FoundationOne Liquid assay can help test and identify a broader population of people with advanced NSCLC who may benefit from Alecensa, for whom current diagnostic tests are not suitable, such as for those who cannot provide tissue samples due to insufficient or absent tumor tissue, or where tissue diagnostics are not available, and validate the clinical utility of blood-based NGS as an additional method to inform clinical decision-making in ALK-positive NSCLC.

In the study, 87.4% (95% CI: 78.5-93.5) of people with advanced NSCLC who were identified by the FoundationOne Liquid biopsy assay to have ALK fusions had a confirmed response to treatment with Alecensa (overall response rate; ORR) as measured by the investigator per RECIST v1.1. This is consistent with the ORR for Alecensa observed in the pivotal phase III ALEX trial, which identified people using tissue-based testing.

When measured using an Independent Review Facility per RECIST v1.1, the confirmed ORR was numerically higher at 92.0% (95% CI: 84.1-96.7). Median progression free-survival and duration of response were not reached after a median follow-up of 12.6 months. The safety profile of Alecensa was consistent with prior clinical trials and post-marketing experience, with no new safety signals observed.

Tecentriq + platinum-based chemo improves PFS in untreated advanced bladder cancer

Tecentriq plus chemotherapy showed a statistically significant improvement in progression-free survival compared with platinum-based chemotherapy alone for the first-line initial treatment of patients with previously untreated locally advanced or metastatic urothelial carcinoma (mUC) eligible and ineligible for cisplatin chemotherapy.

Genentech, a member of the Roche Group, sponsored the phase III IMvigor130 study.

The median PFS of Tecentriq plus chemotherapy compared with platinum-based chemotherapy alone was 8.2 versus 6.3 months; [HR]=0.82, 95% CI: 0.70-0.96; p=0.007.

Encouraging overall survival results were observed for Tecentriq plus chemotherapy compared with chemotherapy alone in the intention-to-treat population, however these data did not reach statistical significance at this interim analysis (median OS=16.0 versus 13.4 months; HR=0.83, 95% CI: 0.69-1.00).

Safety in the Tecentriq plus chemotherapy arm appeared consistent with the known safety profiles of the individual medicines, and no new safety signals were identified with the combination.

“There remains a high unmet need for people with advanced bladder cancer, where chemotherapy alone is the current standard of care. These results reinforce the role of immunotherapy in treating this aggressive disease,” Chief Medical Officer and head of Global Product Development at Roche/Genentech, Sandra Horning, said in a statement.

Additional data from the Tecentriq monotherapy arm were also presented in the ITT population and people with different levels of PD-L1 expression. Encouraging OS results were observed with Tecentriq monotherapy in people with high PD-L1 expression (IC2/3), however these data were not formally tested per the hierarchical design of the trial. Follow-up will continue until the next analysis.

These data were presented at ESMO Sept. 30.

Tecentriq was the first cancer immunotherapy approved in advanced bladder cancer. Tecentriq has accelerated approval from tFood and Drug Administration for treatment of adults with locally advanced or mUC, including those who are not eligible for cisplatin-containing chemotherapy and whose tumors express high levels of PD-L1 (PD-L1–stained tumor-infiltrating immune cells covering $\geq 5\%$ of the tumor area) as determined by an FDA-approved test or are not eligible for any platinum-containing chemotherapy regardless of PD-L1 status.

The accelerated approval also includes the treatment of adults with locally advanced or mUC whose disease had progressed during or following platinum-containing chemotherapy, or within 12 months of receiving chemotherapy before surgery (neoadjuvant) or after surgery (adjuvant). These accelerated approvals are based on tumor response rate and durability of response. Continued approval in these types of bladder cancer may be contingent upon verification and description of clinical benefit in a confirmatory trial.

There are four ongoing phase III studies evaluating Tecentriq alone and in combination with other medicines in early and advanced bladder cancer. Genentech has an extensive development program for Tecentriq, including multiple ongoing and planned Phase III studies, across lung, genitourinary, skin, breast, gastrointestinal, gynecological and head and neck cancers. This includes studies

evaluating Tecentriq both alone and in combination with other medicines.

Pfizer reports positive data from late-stage BEACON CRC trial

Results from the phase III BEACON CRC trial show significant improvements in overall survival and objective response rates for the BRAFTOVI Triplet and BRAFTOVI Doublet combination (BRAFTOVI and cetuximab), compared to cetuximab plus irinotecan-containing regimens (Control), and provide analysis of the efficacy and safety of the BRAFTOVI Triplet compared to the BRAFTOVI Doublet.

The trial evaluates the combination of Braftovi (encorafenib), Mektovi (binimetinib), and cetuximab (Braftovi Triplet), in patients with advanced BRAFV600E-mutant metastatic colorectal cancer, following one or two lines of therapy.

Pfizer sponsors the trial.

BRAFTOVI Triplet showed a median OS of 9.0 months, compared to 5.4 months for Control. An improved ORR of 26% was observed in BRAFTOVI Triplet compared to 2% for Control.

These data were presented Sept. 30 at ESMO.

The company expects to submit the results of the trial for marketing approval in the United States in Q4 2019.

X4 reports positive data from phase IIa study of Mavorixafor + Axitinib in advanced clear cell RCC

Combination therapy with mavorixafor and axitinib (Inlyta) demonstrated

clinical improvement with encouraging median progression free survival in a heavily pretreated advanced clear cell renal cell carcinoma patient population.

The results come from the phase IIa portion of X4 Pharmaceuticals Inc.'s open-label phase I/II clinical trial of mavorixafor (X4P-001) in combination with approved tyrosine kinase inhibitor axitinib in patients with ccRCC.

Axitinib was generally well tolerated with a manageable safety profile. Of the 65 patients in the trial, 49 patients (or 75%) received mavorixafor + axitinib as a third-to ninth-line therapy, having received between two and eight prior therapies with a TKI, immuno-oncology agent, or other systemic therapy. Fifty-seven of the 65 patients in the trial (or 88%) had an intermediate or poor prognosis.

Data were presented Sept. 30 at ESMO.

Overall mPFS across clinically evaluable patients receiving mavorixafor + axitinib (n=62) was 7.4 months. Predefined subpopulations examined patients with immediate prior TKI and IO treatment. Patients treated in the subgroup with immediate prior TKI therapy (n=34) demonstrated an objective response rate (ORR) of 18% and an increased mPFS of 7.4 months.

This is a greater than 50% improvement from the 4.8-month historical mPFS with axitinib alone. Patients treated with mavorixafor + axitinib in the subgroup with immediate prior IO therapy (n=18) had an ORR of 61% and an increased mPFS of 11.6 months. In addition, eight of the 65 patients remain on the combination therapy today, with durations of treatment of 17 months or longer. Results suggest mavorixafor may enhance clinical response to axitinib and other TKIs that target tumor angiogenesis, as well as immunotherapy agents.

“In recent years a growing number of vascular endothelial growth factor (VEGF) TKI-based therapies (e.g., axitinib

+ pembrolizumab), have improved outcomes for patients with ccRCC. Despite these advances, most patients eventually develop resistance to therapy, and new treatment options are necessary to meet this unmet medical need,” lead investigator David F. McDermott, of Beth Israel Deaconess Medical Center, Harvard Medical School, said in a comment. “In this trial of mavorixafor, a novel CXCR4 pathway inhibitor, and axitinib in patients with metastatic ccRCC who had failed prior therapy, the combination was well tolerated and the anti-tumor activity was encouraging. We look forward to confirming the efficacy of mavorixafor in a randomized trial.”

This phase I/II, multi-center, open-label trial of mavorixafor in combination with axitinib included 65 patients with histologically confirmed advanced ccRCC, all of whom received at least one prior systemic therapy. The safety analyses included 65 patients from phases I/II who were treated with 400 mg mavorixafor (200 mg twice daily or 400 mg once daily) + 5 mg axitinib twice daily. Treatment responses were assessed using RECIST v1.1 (a validated set of criteria to assess changes in tumor burden), every eight weeks from day one for 80 weeks, and then every 12 weeks thereafter, by blinded, independent central review.

Half of cancer patients who enter tobacco treatment program quit smoking, study shows

Comprehensive tobacco treatment can help cancer patients quit and abstain from smoking, according to a study from MD Anderson Cancer Center.

The prospective study analyzed 3,245 smokers treated in MD Anderson’s Tobacco Treatment Program between 2006 and 2015. At three, six and nine-month follow-ups, smoking abstinence

rates averaged 45%, 46% and 44%, respectively.

The study, described as the largest smoking cessation study of cancer patients to date, was published in [*JAMA Network Open*](#) Sept. 27.

Based on these findings, the authors advocate for full integration of comprehensive tobacco treatment into the oncological setting.

While the study was not designed as a randomized clinical trial and did not compare different types of smoking cessation programs, past studies have shown quitlines or other minimal interventions have abstinence rates of 20% or less. As with quitlines, abstinence rates for the Tobacco Treatment Program were self-reported and were not regularly biochemically verified.

“Patients deserve the absolute best opportunity we can give them to quit smoking,” lead author, Behavioral Science Chair and Director of the Tobacco Treatment Program Paul Cinciripini, said in a statement. “Based on our data, we recommend offering comprehensive smoking cessation to cancer patients as a clinical standard of care.”

MD Anderson’s program provides personalized tobacco treatment to nearly 1,200 new patients every year. Since 2013, patients have been automatically referred to the program through an electronic questionnaire used in all institutional clinics.

Program staff contact every new patient who self identifies as a smoker. Most patients who agree to participate in the comprehensive program receive both intensive counseling and proactive medication management.

“We tailor nicotine replacement therapy recommendations to each individual and provide support through behavioral counseling sessions over eight to 12 weeks following their initial consulta-

tion,” Professor of Behavioral Science and Medical Director of the Tobacco Treatment Program, Maher Karam-Hage, said in a statement. “Through this combined approach, we’ve seen effective results in cessation and abstinence.”

Cinciripini and Karam-Hage received grant support and medication (Chantix) from Pfizer to conduct smoking cessation trials, and have participated in two multisite trials sponsored by Pfizer.

Average cost per quit ranges from \$1,900 to \$2,500 at MD Anderson. Participants receive treatment services for free, as the Tobacco Treatment Program is funded primarily through Texas Tobacco Settlement Funds awarded through the Tobacco Master Settlement. The authors note this funding arrangement is progressive and could serve as a model for other states.

The MD Anderson program is open to employees as well. The study did not find a difference in abstinence rates between cancer patients and non-patients. For cancer patients, smoking also negatively impacts survival and treatment.

“Quitting at time of diagnosis increases the chance of survival by 30% to 40%. Patients also have less chance of a recurrence or secondary cancer if they quit. They will have fewer side effects and their treatments will be more effective. Longer term, they will enjoy a better quality of life,” said Assistant Professor of Behavioral Science Diane Beneventi.

This study received funding support from the State of Texas Tobacco Settlement funds and from MD Anderson’s Cancer Center Support Grant (CA016672).

Lynparza meets primary goal in late-stage study

Lynparza (olaparib) demonstrated statistically significant and clinically meaningful improvement in the primary end-

point of radiographic progression-free survival in certain tumors.

Lynparza reduced the risk of disease progression or death in the phase III PROfound clinical trial results by a median of 7.4 months versus 3.6 months for those receiving abiraterone or enzalutamide; Lynparza reduced the risk of disease progression or death by 66% for these men.

The drug is being developed by Astra-Zeneca and Merck.

The trial also met key secondary endpoint of rPFS in overall HRRm population, where Lynparza reduced the risk of disease progression or death by 51% and improved rPFS to a median of 5.8 months versus 3.5 months for those receiving abiraterone or enzalutamide.

Secondary endpoint of median time to pain progression was not reached.

PROfound showed a confirmed overall response rate, a key secondary endpoint of 33.3% for Lynparza versus 2.3% for abiraterone or enzalutamide in patients with BRCA1/2 or ATM mutations.

Safety and tolerability profile of Lynparza in the PROfound trial was in line with that observed in prior clinical trials.

DRUGS & TARGETS



NCI TRIALS



Keytruda approved as monotherapy in China for NSCLC

The National Medical Products Administration in China approved Merck's Keytruda as monotherapy for the first-line treatment of patients with locally advanced or metastatic non-small cell lung cancer whose tumors express PD-L1, with no EGFR or ALK genomic tumor aberrations.

Keytruda is the first anti-PD-1 therapy approved in China as both monotherapy and in combination with chemotherapy for the first-line treatment of patients with NSCLC.

NCI Trials for October

The National Cancer Institute Cancer Therapy Evaluation Program approved the following clinical research studies last month.

For further information, contact the principal investigator listed.

Phase I - ABTC-1804

Determining the Dose of Regadenoson Most Likely to Transiently Alter the Integrity of the Blood-Brain Barrier in Patients with High Grade Gliomas

Adult Brain Tumor Consortium
Grossman, Stuart Alan
(410) 955-8837

Phase II - ACNS1723

A Phase 2 Study of Dabrafenib (NSC# 763760) with Trametinib (NSC# 763093) After Local Irradiation in Newly-Diagnosed BRAF V600-Mutant High-Grade Glioma (HGG) (IND# 145355)

Children's Oncology Group
Lulla, Rishi Ramesh
(401) 444-5171

Phase III - A221803

Mepitel Film for the Reduction of Radiation Dermatitis in Breast Cancer Patients Undergoing Post-Mastectomy Radiation Therapy: A Randomized Phase III Clinical Trial

Alliance for Clinical Trials in Oncology
Corbin, Kimberly S.
(507) 284-2669

Phase Other - WF-1805CD

Implementation and Effectiveness Trial of HN-STAR

Wake Forest NCORP Research Base
Weaver, Kathryn E.
(336) 713-5062