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Review

Research gaps in evaluating the relationship of meat and health

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ABSTRACT

Humans evolved as omnivores and it has been proposed that cooking meat allowed for evolution of larger brains that has led to our success as a species. Meat is one of the most nutrient dense foods, providing high-quality protein, heme iron, zinc, and vitamins B_6 and B_{12}. Despite these advantages, epidemiologic studies have linked consumption of red or processed meat with obesity, type 2 diabetes, cardiovascular diseases, and cancers of multiple organs. Most observational studies report small, increased relative risks. However, there are many limitations of such studies including inability to accurately estimate intake, lack of prespecified hypotheses, multiple comparisons, and confounding from many factors – including body weight, fruit/vegetable intake, physical activity, smoking, and alcohol – that correlate significantly either positively or negatively with meat intake and limit the reliability of conclusions from these studies. The observational studies are heterogeneous and do not fulfill many of the points proposed by AB Hill in 1965 for inferring causality; his most important factor was strength of the association which in dietary studies is usually <1.5 but is not considered adequate in virtually all other areas of epidemiology outside nutrition. Accepting small, statistically significant risks as "real" from observational associations, the field of nutrition has a long list of failures including beta-carotene and lung cancer, low-fat diets and breast cancer or heart disease that have not been confirmed in randomized trials. Moderate intake of a variety of foods that are enjoyed by people remains the best dietary advice.

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1. Introduction

Although one can only infer what early hominins ate, there is considerable evidence that meat consumption contributed significantly to the diet and that cooking was an essential development once controlled fire was available 800,000 years ago and perhaps for more than 2 million years (Carmody & Wrangham, 2009; Luca, Perry, & Di Rienzo, 2010). This speculation is based on stable isotope ratios, dental morphology, dental wear patterns, and relative volume of the various intestinal segments (Milton, 2003) all of which indicate a diet of mixed origins in contrast to non-human primates that subsist mostly on plant foods even though most of them consume meat sporadically. Domestication of beef cattle occurred more than 8500 years ago and it is logical to assume that meat consumption increased compared to when animals were hunted. Although the U.S. Department of Agriculture (USDA) maintains per capita food production data back to only 1909, there are many books that point to higher beef consumption in the U.S. during the nineteenth century, which has led to estimates of intake of two to three times what is currently consumed when chronic, non-communicable diseases were rare (Smil, 2002). The consumption of cooked meat results in greater intake of high quality protein that is denatured by heat and therefore provides more digestible protein, more energy availability, and an increase in brain size that is thought to be

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causally related to the evolutionary separation of humans from other primates. In modern times, few people in developed countries have to worry about either protein or caloric adequacy but there are at least one billion people on the planet who do not have adequate intakes of protein, calories, or some of the nutrients that meat supplies in abundance such as vitamins B_6 and B_{12}, zinc, and iron in the biologically more available heme form. Meat is clearly a nutrient dense food with beef, the most popularly consumed meat in the United States, having the highest concentration of vitamins and minerals (Fig. 1).

While meat is a more nutrient dense food than most plant foods and is consumed on a regular basis by the majority of the population, there is concern raised by many observational studies that high intake of red and/or processed meat intake is associated with chronic diseases such as obesity, type 2 diabetes, cardiovascular disease, and a variety of cancers. As a result of such observational studies, many governmental and non-governmental health agencies have recommended restriction of red and/or processed meat intake (Superior Health Council, 2013; World Cancer Research Fund/American Institute for Cancer Research, 2012). The two referenced organizations recommend maximum weekly consumption of red meat at 100 g/d and 500 g/wk, respectively; both recommend minimal intake of processed red meat products based on increased risk of colon cancer. This paper will address the limitations of the studies on which those recommendations are based, address the existing research gaps, and try to describe the degree of certainty one can have concerning these putative relationships.

2. Epidemiologic studies in the context of total evidence

It is important to realize that there will almost certainly never be controlled trials of meat consumption (or any other single food) and chronic disease endpoints because of the cost, size of the study sample needed, length of time required, as well as the issue of compliance with dietary advice in both the intervention and control groups. There is also the ethical issue that if meat is considered a risk factor for any disease endpoint based on interpretation of existing data, then it would not be ethical to feed one group of subjects with an amount of meat that would be expected to lead to increased disease. Therefore, most of the data available on which to base dietary recommendations is derived from observational studies of free-living people. It must be acknowledged that cross-sectional studies, which are done at a single time point, do not have the ability to relate cause and effect by themselves. This position was articulated by Hill 50 years ago, who listed nine types of evidence that would help bolster findings from observational studies, and remains well regarded (Hill, 1965); the nine types of evidence include: strength which Hill believed was by far the most important, consistency, specificity, temporality, biological gradient, plausibility, coherence, experiment, and analogy. These considerations are lauded simultaneously to support

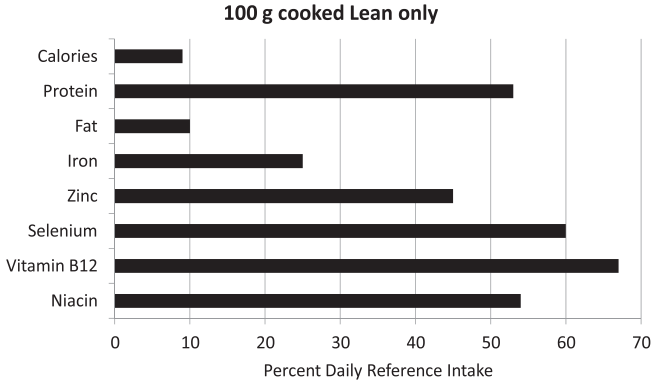

Fig. 1. Percent of U.S. Daily Reference Intakes from a serving of 100 g cooked lean beef tenderloin. Note the ratio of most nutrients to calories which emphasizes the nutrient density of this food.
Source: USDA National Nutrient Database for Standard Reference, Release 27.

their opposing arguments by those who favor or oppose using observational studies alone for drawing conclusions about causality. Hill's considerations are often listed as criteria to fulfill despite the fact that he specifically cautioned against doing so. His argument was that the more types of evidence available, the more likely one was to being able to conclude causality from a relationship. Hill also wrote that the degree of evidence needed to get people to give up sugar and fat should be stronger than replacing a chemical in industrial use when a safer alternative was available. Hill's position has fostered a great deal of debate and critical thinking about these issues for decades.

Among observational studies, case–control studies are now also considered flawed for assessing causality because of the differential recall of diet between cases recently diagnosed with a serious disease and that of controls who do not have that condition. That leaves primarily prospective cohort studies and there is a belief that such studies can predict cause and effect by those in nutritional epidemiology although that view has been challenged by many outside that discipline. Cohort studies are generally designed so that participants usually have no diagnosed serious illnesses and have diet assessed at the beginning of a study, and sometimes, at regular intervals during extended follow-up. This latter distinction is important because those studies that apply only a single determination of dietary intake assume that the diet of participants does not change over the duration of the follow-up which is frequently 10–20 years when chronic diseases are evaluated; shorter-term follow-up studies abound in the literature but are of little value because of the possibility of reverse causality — that is, the presence of undiagnosed disease often results in changes of diet. The assumption that diet does not change markedly over time is almost certainly erroneous. One example from the Nurses' Health Study showed that 77% of women changed their dietary fiber intake by two or more quintiles over only 6 years (Fuchs et al., 1999). Interpretation of those results can provide only two reasonable conclusions that are not mutually exclusive: that the diet changes considerably over time or that the FFQ is simply not reproducible enough to provide certainty about intakes. So that leaves readers with only prospective cohort studies that use routine evaluations of diet every few years as the studies to consider even though this distinction is rarely applied in meta-analyses of this area. It is important also to realize the limitations of assessing dietary intake. This function is dependent upon the accuracy of both food composition databases and the dietary survey instrument. Given the huge number of food products in the marketplace, it is impossible to keep up with changes. For example the USDA food composition database, considered the largest and most accurate in the world, has >8600 foods but the American food supply has up to 100,000 distinct food products many of which are in the marketplace for a short time or have their formulas changed periodically. Some products in the USDA database have not been updated for many years and some compositions are imputed from typical formulations. The USDA database is also used in many other countries that do not have analyses of their own food supplies, potentially making the accuracy of nutrient information from studies in other countries highly suspect.

To enable analysis of large numbers of dietary surveys by machine-scoring, food-frequency questionnaires (FFQs) have become the standard means of evaluating food consumption, although a few studies have used multiple 24-h recalls or multi-day food diaries. Some FFQs do not ask about portion size but only frequency of consumption. Because people with different weights and levels of physical activity have a very large difference in energy requirements, food and nutrient intake in most FFQs are adjusted for total energy intake. While this is logical, a number of studies have clearly shown that the FFQ is poor at determining energy intake. If there is little confidence in the divisor (energy), it is impossible to attribute much certainty to the numerator (a specific food or nutrient). In addition, the standard "validation" of an FFQ has been to determine how well it correlates with intake as measured by 24-h recall. Since recalls are usually $\pm$25% of true intake as determined by doubly labeled water, and FFQs correlate with recalls on