The Mediterranean Diet, the *OGG1* Gene, and Disease Risk: Early Evidence

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ARTICLE INFORMATION

Article history:
Submitted 8 August 2017
Accepted 27 September 2017
Available online 2 January 2018

Keywords:
Cancer
Cardiovascular disease
Mortality
Nutrigenetics
Vegetables

https://doi.org/10.1016/j.jand.2017.09.026

THE RELATIONSHIP BETWEEN EUROPEAN FOOD AND fat consumption trends and coronary heart disease, cancer, stroke, and all-cause mortality has increasingly gained public health attention.[1-3] This increase in attention began with early ecological evidence suggesting a positive association between a Mediterranean-type dietary pattern and health compared to dietary patterns with low intake of olive oil.[1-3] The Mediterranean diet (MedDiet) pattern is not a single dietary pattern, but rather a variation of rural Mediterranean Basin dietary patterns that traditionally share some commonalities.[4] The best known are the Spanish, Greek, and Italian MedDiet patterns, which emphasize fruits, vegetables, unrefined grains and cereals, breads, nuts, seeds, beans, fish, olives, and olive oil, which contribute rich mono-unsaturated and polyunsaturated fat intakes; de-emphasize meat and full-fat dairy intakes, which limits saturated fat intakes; and advocate judicious wine consumption with meals.[4-7] The current 2015-2020 Dietary Guidelines for Americans recommend a "Healthy Mediterranean-Style Eating Pattern"[8] to promote health and protect against common Western diseases, including cardiovascular disease,[7] type 2 diabetes,[9] breast cancer,[10] and cognitive impairment or dementia.[11]

The PREDIMED (Prevención con Dieta Mediterránea) trial tested whether adherence to a single, Spanish-type MedDiet reduced a composite end point of major cardiovascular events (ie, stroke, myocardial infarction, and cardiovascular death) in approximately 7,447 individuals at high-risk for cardiovascular disease (CVD) living in Spain. Participants were assigned to one of three study arms and were counseled to follow a MedDiet supplemented with 1 L/wk extra-virgin olive oil or a MedDiet supplemented with 30 g/day nuts or a reduced-fat diet (control group) during the entire study period. Participants were followed for 4.8 years. Due to an impressive approximately 30% reduction in its trial composite end points, the PREDIMED trial was terminated early, which has left residual concerns about its reproducibility, control group, and the generalizability of the modified Spanish-type MedDiet pattern.[7,12-16] Regardless, the results are striking, as most randomized, controlled trials fail to support diet-based interventions as effective strategies for reducing disease risks (eg, cancer).[14,17] The PREDIMED trial was arguably the largest successful dietary intervention in recent history. It is a valuable hypothesis-generating and testing resource, spanning more than 200 scientific papers to date, and will likely be so for many years.

In this issue of the *Journal*, Corella and colleagues[18] report on a significant association between participants in the PREDIMED study who were homozygous carriers of the Cys326 variant of oxyguanine glycosylase 1 (*OGG1*), having an 8-oxoguanine DNA glycosylase with lower DNA repair capacity (*OGG1*-rs1052133 [Cys326Cys]), and higher all-cause mortality risk (hazard ratio 1.69; 95% CI 1.09 to 2.62; P=0.018) presumably attributed to CVD influences (hazard ratio 3.31; 95% CI 1.68 to 6.53; P=0.001) compared with Ser carriers. No statistically significant association was detected between *OGG1* Cys326Cys genotype carriers and cancer-specific mortality (hazard ratio 1.07; 95% CI 0.47 to 2.45; P=0.867), despite a higher frequency of cancer deaths compared to CVD deaths. However, subgroup analyses suggested a >3.2-fold higher cancer mortality risk in younger participants only, when adjusted for baseline age (<66.5 years). Because the authors examined just one single nucleotide polymorphism of the *OGG1* gene, future exploration of this gene–diet interaction remains possible. While low vegetable intake (<314 g/day) was associated with increased cardiovascular mortality risk (P<0.001) in *OGG1* Cys326Cys carriers, high total vegetable intake (>314 g/day or 2.5 servings/day) was somewhat protective in reducing CVD-specific mortality risk (P=0.046).

Corella and colleagues[18] push the narrative on gene–diet interaction to health associations further by providing evidence of a putative pathway from *OGG1* single nucleotide polymorphism carriage and vegetable intake to human mortality. However, registered dietitian nutritionists and nutrition and dietetic technicians, registered, are reminded that the clinical utility of gene–diet interaction might be premature, as researchers embrace a rapidly expanding genetics revolution. Similarly, researchers must be very clear about the limitations of their study findings and the need for replication of results before real conclusions can be drawn. Corella and colleagues[18] report their associational findings in

a single DNA repair gene using the Spain-based PREDIMED participant population. Current allelic penetrance data obtained from the National Institutes of Health database of single nucleotide polymorphisms suggest globally limited data availability at individual or population levels for *OGG1*,[19] so the frequency of carrying this allele outside of the study population is largely unknown. The idea that higher vegetable intake can protect you from "bad" genes is not new, but despite increasing numbers of over-the-counter "nutrigenomics" tests available to consumers, their use should be interpreted with the same caution that Corella and colleagues state in their concluding sentence, that "…replication of these results in other studies is needed… ."[18] Even though results like these are the foundation on which great scientific advances are made, these results take years for responsible scientists to confirm, as these authors suggest.

There are many challenges inherent to testing the effects of dietary compounds, the exposures of which vary with time, are low dose, and generally act upon biologic targets at lower potencies than drugs.[20-22] These challenges, coupled with difficulties in accurately measuring food intake,[20-24] have reduced the speed at which our scientific field builds strong, consistent evidence supporting clear gene–nutrient interactions.[25] Although the literature is cluttered with single studies identifying a gene–diet interaction lacking replication or validation, there are prominent examples of well-supported gene–nutrient interactions, including dietary folate methyltetrahydrofolate reductase–gene interactions.[26] Nutrition scientists and dietetics professionals should be pleased with the thoughtful analysis and cautionary interpretation provided by Corella and colleagues, as we look forward to more studies to come.

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STATEMENT OF POTENTIAL CONFLICT OF INTEREST

No potential conflict of interest was reported by the authors.

FUNDING/SUPPORT

Preparation of this article was supported by the National Cancer Institute and the Office of Disease Prevention, National Institutes of Health, Bethesda, MD.