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# Effects of the Ser326Cys Polymorphism in the DNA Repair *OGG1* Gene on Cancer, Cardiovascular, and All-Cause Mortality in the PREDIMED Study: Modulation by Diet

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**ABSTRACT**

**Background** Oxidatively induced DNA damage, an important factor in cancer etiology, is repaired by oxyguanine glycosylase 1 (*OGG1*). The lower repair capacity genotype (homozygote Cys326Cys) in the *OGG1*-rs1052133 (Ser326Cys) polymorphism has been associated with cancer risk. However, no information is available in relation to cancer mortality, other causes of death, and modulation by diet.

**Objective** Our aim was to evaluate the association of the *OGG1*-rs1052133 with total, cancer, and cardiovascular disease (CVD) mortality and to analyze its modulation by the Mediterranean diet, focusing especially on total vegetable intake as one of the main characteristics of this diet.

**Design** Secondary analysis in the PREDIMED (Prevención con Dieta Mediterránea) trial is a randomized, controlled trial conducted in Spain from 2003 to 2010.

**Participants/setting** Study participants (n=7,170) were at high risk for CVD and were aged 55 to 80 years.

**Intervention** Participants were randomly allocated to two groups with a Mediterranean diet intervention or a control diet. Vegetable intake was measured at baseline.

**Main outcome measures** Main outcomes were all-cause, cancer, and CVD mortality after a median follow-up of 4.8 years.

**Statistical analyses** Multivariable-adjusted Cox regression models were fitted.

**Results** Three hundred eighteen deaths were detected (cancer, n=127; CVD, n=81; and other, n=110). Cys326Cys individuals (prevalence 4.2%) presented higher total mortality rates than Ser326-carriers ($P$=0.009). The multivariable-adjusted hazard ratio for Cys326Cys vs Ser326-carriers was 1.69 (95% CI 1.09 to 2.62; $P$=0.018). This association was greater for CVD mortality ($P$=0.001). No relationship was detected for cancer mortality in the whole population (hazard ratio 1.07; 95% CI 0.47 to 2.45; $P$=0.867), but a significant age interaction ($P$=0.048) was observed, as Cys326Cys was associated with cancer mortality in participants <66.5 years ($P$=0.029). Recessive effects limited our ability to investigate Cys326Cys×diet interactions for cancer mortality. No statistically significant interactions for total or CVD mortality were found for the Mediterranean diet intervention. However, significant protective interactions for CVD mortality were found for vegetable intake (hazard ratio interaction per standard deviation 0.42; 95% CI 0.18 to 0.98; $P$=0.046).

**Conclusions** In this population, the Cys326Cys-*OGG1* genotype was associated with all-cause mortality, mainly CVD instead of cancer mortality. Additional studies are needed to provide further evidence on its dietary modulation.

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DNA MOLECULES ARE EXPOSED TO THE ATTACK OF DNA-damaging agents,[1] among them reactive oxygen species.[2] Oxidatively induced DNA damage can be both mutagenic and cytotoxic,[3] and has been implicated in the etiology of cancer,[4] neurodegenerative diseases,[5] and overall aging.[6] Hydroxyl radicals preferentially react with the C8 atom of purines in DNA to generate 8-oxo-7,8-dihydroguanine, 8-oxo-7,8-dihydroadenine, and

formamidopyrimidines.[7] The accumulation of unrepaired DNA damage can cause genetic instability and has deleterious effects on cell function.[8] 8-oxo-7,8-dihydroguanine is a critical mutagenic lesion because of its propensity to mispair with A during DNA replication.[7] Repair of oxidatively damaged bases occurs primarily via the DNA base excision repair pathway.[2] In the first step of this type of repair, damaged bases are removed from DNA by DNA glycosylases.[9] The oxyguanine glycosylase 1 (*OGG1*) is the human DNA glycosylase responsible for removal of the highly mutagenic 8-oxo-7,8-dihydroguanine from DNA.[7] The *OGG1* gene is located in chromosome 3p26.2, and this region has frequently been detected as deleted in various tumors, suggesting the loss of this gene as a possible contributor to carcinogenesis.[7,10-13]

The most studied polymorphism in the human *OGG1* gene is the rs1052133 (Ser326Cys), a C to G transversion at nucleotide 1245 in exon 7, leading to a serine to cysteine substitution at residue 326.[14] This variant is functional and it has been shown that the Cys326 protein has weaker 8-hydroxyguanine-repair capacity than the Ser326 protein.[15-17] The deactivation of the *OGG1* gene or the presence of a less-active variant, such as the Cys326, can lead to a higher risk of cancer and oxidation-related pathologies.[7,13,18] Consequently, this polymorphism has been analyzed as a risk factor in several cancers[19-25] (ie, breast, prostate, lung, colorectal, aerodigestive, gastric, and bladder). The results of meta-analyses for each location are heterogeneous,[21-25] but where there is more consensus is in the significant association of the Ser326Cys polymorphism with greater overall risk of cancer when the different locations are pooled.[26,27] Zou and colleagues,[26] in a meta-analysis including 152 case-control studies, concluded that the Cys variant was strongly associated with higher cancer risk. Interestingly, the cancer risk was higher in homozygous individuals for the Cys variant, suggesting a recessive pattern. This observation agrees with several functional studies showing that only homozygous carriers of the Cys allele showed a significantly lower DNA repair activity compared with Ser326Ser.[16,18] A potential source of the observed heterogeneity found among studies may be the exposure to different environmental factors[28-31] (ie, mainly vegetable intake and other dietary factors).

The Ser326Cys *OGG1* polymorphism has also been associated with a greater risk of atherosclerosis[32,33] and incidence of cardiovascular disease (CVD),[34,35] although there have been very few studies that have specifically focused on cardiovascular phenotypes.

Although many studies have analyzed the influence of the *OGG1* Ser326Cys polymorphism on cancer risk, few have analyzed its influence on mortality due to cancer. Moreover, if the *OGG1* gene also makes an important contribution to other pathologies, such as CVDs, there is compelling interest in knowing whether, in the same cohort, this gene has a greater influence on mortality due to cancer or on mortality due to CVD. The aims of this study were: (1) to analyze the influence of the *OGG1* Ser326Cys polymorphism on cancer mortality, cardiovascular mortality, and total mortality in a high cardiovascular risk Mediterranean population, and (2) to investigate the possible modulation by diet by analyzing the Mediterranean diet (MedDiet) intervention, as well as focusing on total vegetable intake at baseline as one of the main characteristics of the MedDiet.

### RESEARCH SNAPSHOT

**Research Question:** Is the lower DNA-repair capacity genotype (homozygous individuals for the Cys326 allele) in the oxyguanine glycosylase 1-rs1052133 (Ser326Cys) polymorphism associated with cancer mortality or other causes, and are these associations modulated by Mediterranean diet or vegetable intake?

**Key Findings:** In the PREDIMED dietary intervention trial including 7,170 participants, the Cys326Cys-*OGG1* genotype was associated with higher total mortality, mainly cardiovascular mortality. For cardiovascular and total mortality, no statistically significant interactions were found with the Mediterranean diet intervention. However, when vegetable intake was considered, significant interactions decreasing the risk for cardiovascular mortality in homozygous individuals with higher intake were detected.

## METHODS

The current study was conducted within the framework of the PREDIMED (Prevención con Dieta Mediterránea) trial, the design of which has been described in detail elsewhere.[36] Briefly, the PREDIMED study is a multicenter, randomized, controlled clinical trial aimed at assessing the effects of the MedDiet on the primary cardiovascular prevention.[37] This study was registered at controlled-trials.com (http://www.controlledtrials.com/ISRCTN35739639). Here, 7,170 participants (from a total of 7,447) were included, from whom DNA was isolated and the *OGG1*-rs1052133 (Ser326Cys) polymorphism determined. Briefly, from October 2003 to June 2009, physicians in primary care centers located in several Spanish regions selected high-CVD-risk participants. Eligible participants were community-dwelling adults at high risk for CVD (age 55 to 80 years for men; age 60 to 80 years for women) who met at least one of two criteria: diabetes or three or more CVD risk factors (hypertension, dyslipidemia, overweight or obesity, current smoking, or a family history of premature coronary heart disease).[36] Exclusion criteria were the presence of any severe chronic illness, previous history of CVD, alcohol or drug abuse, and history of allergy or intolerance to olive oil or nuts. Individuals with incident cancer undergoing treatment were excluded, but individuals that reported having had some form of cancer in previous years but who had no clinical signs of cancer at the time of enrollment were not excluded.

Participants were randomly assigned to these interventions: a MedDiet (two groups, one supplemented with extra-virgin olive oil and the other with nuts) and a control group (advised to follow a low-fat diet). Randomization was performed by means of a computer-generated random-number sequence (randomly assigned in a 1:1:1 ratio to one of three groups). Participants assigned to both MedDiet groups received intensive training to follow the