

Temporal trends in colorectal cancer mortality in Greece, 2014-2022: a Joinpoint regression analysis

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Globally, colorectal cancer (CRC) is projected to account for 1.6 million deaths annually by 2040, with an incidence strongly correlated with the Human Development Index and the adoption of westernized lifestyles [1]. Against this backdrop, the availability of reliable national mortality data is not merely an academic exercise: it underpins screening policy, guides resource allocation, and allows countries to benchmark their performance against regional peers. For Greece, however, such data have been absent. The country operates within a European landscape that has increasingly moved toward organized, population-based CRC screening, yet for the entire period between 2014 and 2022 Greece relied exclusively on opportunistic colonoscopy, with no systematic recording of screening uptake. A national CRC screening program has recently been launched, but evidence on its performance is not yet available. In this context, the analysis by Papastergiou *et al* [2] is not simply the first of its kind in Greece: it is the essential baseline against which the impact of that incoming program will eventually be measured.

Drawing on death registry data from the Hellenic Statistical Authority (ELSTAT) and applying Joinpoint regression, Papastergiou *et al* analyzed 24,973 CRC-related deaths recorded in Greece between 2014 and 2022. The headline finding is reassuring in its modesty: overall age-adjusted mortality rates (AAMRs) were essentially stable, declining non-significantly from 10.7 to 10.2 per 100,000 over the study period. The picture diverges sharply by sex.

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Among women, AAMRs fell significantly from 8.4 to 7.4 per 100,000 (Annual Percent Change [APC]: -1.02 , $P=0.03$), while in men the decline was negligible and non-significant (13.7 to 13.6; APC: -0.35 , $P=0.48$). Most strikingly, crude mortality rates in men under 45 years exhibited a biphasic pattern: a significant decline from 2014-2017 (APC: -21.91 , $P=0.02$) was followed by a sharp and statistically significant reversal from 2017-2022 (APC: $+18.90$, $P=0.007$). A non-significant upward trend was also observed in men aged 45-59 throughout the study.

The sex differential in CRC mortality is not unique to Greece, but it is important to understand. Male predominance reflects a convergence of biological, behavioral and systems-level factors: anatomical and molecular differences in tumor biology, differential exposure to lifestyle risk factors such as smoking and alcohol, and consistently lower rates of adherence to CRC screening among men [3]. That the decline in Greece was statistically significant only in women aligns with European-level predictions for 2024, which anticipated a greater proportional mortality reduction for women than for men [4]. Yet here lies a critical interpretive constraint that deserves explicit recognition: Mortality trends alone cannot show whether cancer control is improving, because they do not distinguish the effects of prevention, earlier diagnosis, and treatment. Critically, a stable mortality rate can carry radically different implications depending on what incidence is doing simultaneously. If CRC incidence in Greece was *rising* between 2014 and 2022 while mortality held steady, this would constitute a genuinely favorable signal—more cancers being detected and successfully treated. If incidence was *falling*, stable mortality would instead be alarming, suggesting a worsening case-fatality ratio and potentially later-stage diagnosis. If incidence was *also stable*, the system is simply holding its ground. Without national incidence data, the paper cannot distinguish between these three scenarios, and the true trajectory of CRC outcomes in Greece remains fundamentally ambiguous.

The most clinically relevant finding in the paper is nonetheless the rising CRC mortality in young men, and it deserves contextualization beyond Greek borders. Early-onset CRC disease arising in individuals under 50 has been increasing across Europe and North America for decades, driven by rising rates of obesity, sedentary lifestyles, and dietary shifts toward high consumption of processed food [5]. Within Greece, data from the Regional Cancer Registry of Crete documented a significant rising trend of CRC incidence in adults under 50, with a predicted further increase of 42.8% from 2022-2030 [6]. The present national mortality data are therefore internally

consistent with existing Greek incidence data and align with a global epidemiological shift. Early-onset CRC is not only more common than it was: it tends to present at a more advanced stage because of longer pre-diagnostic delays, and it affects individuals at the height of their productive and family lives [7]. The United States has already responded by lowering its average-risk screening threshold from 50 to 45 years [8]. In Europe, screening programs remain largely targeted at the 50-74 age group [9], and whether that threshold remains appropriate for Greece's evolving epidemiology warrants active monitoring as the new national programs matures.

Any enthusiasm must be tempered by methodological caution. The absolute number of CRC deaths in men under 45 is small—only 13 in 2017, the very year from which the *post hoc* APC of +18.90% is calculated—and the wide confidence interval (6.22 to 58.70) reflects this fragility. A sensitivity analysis excluding the COVID-19 years (2020-2022) is absent, which matters because the joinpoint falls in 2017, three years before the pandemic, making it impossible to separate a pre-existing trend from any pandemic-related acceleration in diagnostic delay.

More importantly, in the absence of national incidence data, this study can describe population-level patterns in cancer mortality, but it cannot determine whether observed differences are driven by variation in cancer occurrence, stage at diagnosis, access to care, treatment effectiveness, or survival. Screening history, stage at diagnosis, treatment access and comorbidity burden are all unobserved. This is not a criticism of the authors, who have used the only nationally representative data available. It is, rather, a pointed reminder that Greece's death registry, however rigorously maintained, is an instrument with one dial. A full assessment of CRC control requires a second instrument: a national cancer registry capable of capturing incidence.

What, then, should clinicians and policymakers take away from this landmark, if necessarily incomplete, analysis? Three messages stand out. First, the declining mortality trend in women and the broadly stable overall rates are genuinely encouraging for a country that achieved them without organized screening, suggesting that the forthcoming national program represents a real additional opportunity to drive mortality down further. Second, the persistent failure to reduce mortality in men demands that the new program be explicitly designed with male engagement in mind: invitation strategies, choice of screening modality, and recall systems should

account for the well-documented lower participation of men in preventive healthcare. Third, and most importantly, the rising mortality signal in young men and the unresolvable ambiguity around the mortality-to-incidence ratio both point to the same structural gap: Greece needs a national cancer registry. Without systematic, nationally representative incidence data, it will be impossible to assess whether the new screening program is reducing the stage at diagnosis, and impossible to determine whether the early-onset signal reflects a genuine rise in incidence, a worsening case-fatality ratio, or both. The work of Papastergiou and colleagues provides the mortality half of an equation that Greek public health has yet to complete. Investing in the infrastructure to provide the other half is not a research priority: it is a prerequisite for evidence-based cancer policy.

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