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ORIGINAL RESEARCH

Regional disparities in cancer mortality across the rural-urban axis: a case study from north-eastern Greece

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ABSTRACT

Introduction: The aim of this study was to identify differences in cancer mortality in north-eastern Greece, to describe potential drivers operating at the population level and to propose practical interventions and mitigation strategies.

Methods: Cancer mortality data were collected from local registries using the WHO 10th edition of *International Classification of Disease* (ICD-10). The direct standardization method was used to address demographic differences in the two regions, with the Standard European Population as reference. Rate ratios (RR) were employed for comparisons and 95% confidence intervals (95%CI) were calculated according to the Poisson approximation method.

Results: An increased risk of digestive system cancers (excluding liver neoplasms) was observed in rural versus urban areas (RR=1.25, 95%CI=1.02–1.54). Stomach cancer, in particular, was more prevalent in the older cohorts (>65 years), suggesting a historical epidemiological perspective. A more pronounced discrepancy was observed for prostate cancer mortality (RR=1.86, 95%CI=1.10–3.14), indicating a strong positive correlation with rurality.

Conclusions: Cancer mortality disparities have been observed between rural and urban regions of north-eastern Greece. Health promotion and education, including improved access to medical facilities and early cancer screening, can help mitigate the burden and extend survival rates. Decreasing cancer staging at the time of diagnosis and reversing social and economic inequalities is key for combating these types of malignancy.

Key words: cancer mortality, north-eastern Greece, rural-urban disparities, statistics.

Introduction

Differential patterns of cancer incidence and mortality have been observed between rural and urban communities around the world[1-3]. Social, economic, cultural, occupational and environmental factors have been suggested as the major driving forces behind these disparities[4-7]. One of the most plausible hypotheses is the potential link between social deprivation and rurality, which is associated with decreased access to health care and specialized treatment[8-10]. This discrepancy is realized both in terms of secondary prevention (early cancer screening), as well as at the level of advanced therapeutics that influence disease prognosis and survival rates[11-13].

The traditional belief that agricultural populations live longer and are generally healthier compared to urban dwellers is constantly being challenged by epidemiological studies. Recent demographic data indicate that rural populations around the world are ageing at an accelerating pace[14]. This is increasing the overall burden of chronic disease, including cancer and diabetes[15,16]. Significant health disparities have been recorded for these types of pathologies and well-described socioeconomic variables have been proposed as modifiable risk factors[17].

Epidemiological evidence on cancer mortality for underprivileged populations is important because it can be used to increase health awareness and help orchestrate interventions that mitigate disease impact. There is no doubt that early diagnosis through effective screening can significantly improve survival[17]. Prostate, breast and colorectal adenocarcinomas can be readily detected by digital rectal exam (DRE) and/or prostate-specific antigen (PSA) screening, mammography and colonoscopy, respectively, and this can have a direct impact on disease prevention[18-21].

Within this spectrum of understanding, recording differential patterns of cancer mortality is mandatory for setting priorities in social, temporal and geographic contexts. Small-area epidemiological observations can unmask differences that are otherwise lost in the 'big picture' of national statistics[22]. This changes the agenda from whether it is suitable to use rural–urban disparities in the study of cancer to finding the best way of exploiting the information that emerges from comparisons of this kind[23].

In the present study, two regions of north-eastern Greece that differ markedly were examined, one being predominantly agricultural and the other highly urbanized. Age-standardized mortality ratios were used to address corresponding differences between the two regions and conclusive evidence for the impact of various types of cancer have been devised. Based on these findings, some explanations for the observed discrepancies are suggested and public health interventions associated with the mitigation of the burden of cancer are proposed.

Methods

Mortality data for the period 1999–2008 were collected from the death registries of two regions: region A (*N*=3879 records), which was 92.7% urbanized (National Statistical Authority, 2001 census) and region B (*N*=2237 records), where 14 out of 15 communities were classified as rural. A population is defined as rural when fewer than 2000 residents are reported in the census. Cases involved male and female individuals with permanent residence in either of the two regions. Cause of death was defined according to the WHO's 10th edition of *International Classification of Disease*. Age-standardization was performed by the direct method using the WHO Standard European Population[24] as reference, according to the equation:

$$SDR = \frac{\sum_{i=1} a_i w_i}{\sum_{i=1} w_i}$$

Where $a_i = 10^5 (d_i / y_i)$ d_i are the number of deaths per age group, y_i the corresponding person-years and w_i the number of people in each age group (i) of the standard population.

Calculation of the standard error (SE) was performed according to the equation:

$$S.E. = \sqrt{Var}\text{ , where}$$

$$Var = \frac{\sum_i (a_i w_i^2 \times 100000 / y_i)}{\left(\sum_i w_i\right)^2}$$

Confidence intervals at the 95% level (95%CI) were calculated by the Poisson approximation method:

$$CI(95\%) = SDR \pm Z_{a/2} \times SE(SDR)$$

Finally, for direct comparisons rate ratios were calculated by the formula:

$$(SDR_1 / SDR_2)^{1 \pm (Z_{a/2}/X)}$$

$$\text{where } X = \frac{SDR_1 - SDR_2}{\sqrt{(SE(SDR_1)^2 + SE(SDR_2)^2)}} \text{ and}$$

$$Z_{a/2} = 1.96.$$

Standardized mortality rates for stomach (C16), colorectal (C18–20), pancreatic (C25), liver (C22), bladder (C67), kidney (C64), lung (C34), brain (C71) and lymphatic/hematopoietic (C81–96) cancers, as well as for total cancers of the digestive system (C15–26), including or excluding liver cancer, were analyzed in both sexes. Liver neoplasms were excluded from digestive system cancers, due to the possibility of secondary localization (metastasis) and other risk factors such as viral hepatitis and liver cirrhosis, which may artificially increase their overall impact. Moreover, standardized rates for prostate cancer (C61) were computed for males, and breast (C50), endometrial (C54) and ovary (C56) cancer for females.

All calculations were conducted in Microsoft Excel and the Statistical Package for the Social Sciences v15 (IBM; http://www.spss.com).

Ethics approval

This study has been approved by the Municipality of Evros Ethical Committee (Prot. No. 1441, 24-11-2008) and fully conforms to the provisions of the Declaration of Helsinki.

Results

Crude and standardized, all cause-mortality comparisons for the two regions are given in Table 1. There was no overall effect of rurality/urbanicity on all cause mortality (RR=1.05, 95%CI=0.89–1.14). Moreover, there were no statistically significant differences between the two regions as regards circulatory diseases (I00–I99), respiratory diseases (J00–J99), infectious diseases (A00–B99) and external causes and injuries (V01–Y98).

Table 2 shows the age-standardized mortality per 100 000 person-years for various types of cancer in region A and region B. Comparisons are illustrated by rate ratios and associated 95%CI. Statistically significant differences were observed for cancers of the digestive system, excluding liver neoplasms (RR=1.02, 95%CI=1.02–1.54). Liver neoplasms were excluded from digestive system cancers, due to the possibility of secondary localization (metastasis) and other risk factors such as viral hepatitis and liver cirrhosis, which may artificially increase their overall impact. Mortality from stomach, colorectal, bladder and lymphatic/hematopoietic cancers, as well as liver, kidney and lung cancer, did not differ statistically between the two regions.

Prostate cancer mortality was positively and strongly associated with rurality (RR=1.86, 95%CI=1.10–3.14). Conversely, no significant differences were recorded for breast, ovarian and endometrial cancer among rural and urban females. Moreover, there were no other sex-specific disparities in cancer mortality for any other type of malignancy (Table 3).

Detailed analysis of age-specific cancer mortality produced some notable results (Fig1). The incidence of stomach cancer in rural areas was significantly elevated in the older age groups (>65 years). In contrast, there were no liver and lung cancer cases in younger cohorts of region A.

Table 1: General all-cause mortality per 100 000 person years (both sexes)

Ratio type	Region A (rural)	Region B (urban)	Rate ratio	95%CI
CDR	1181.2	725.59	1.63	1.32–1.76
SDR	750.72	711.67	1.05	0.89–1.14

CI, confidence interval. CDR, crude death ratio. SDR, age-standardized death ratio

Table 2: Rural–urban disparities in cancer mortality: age-standardized rates and ratios

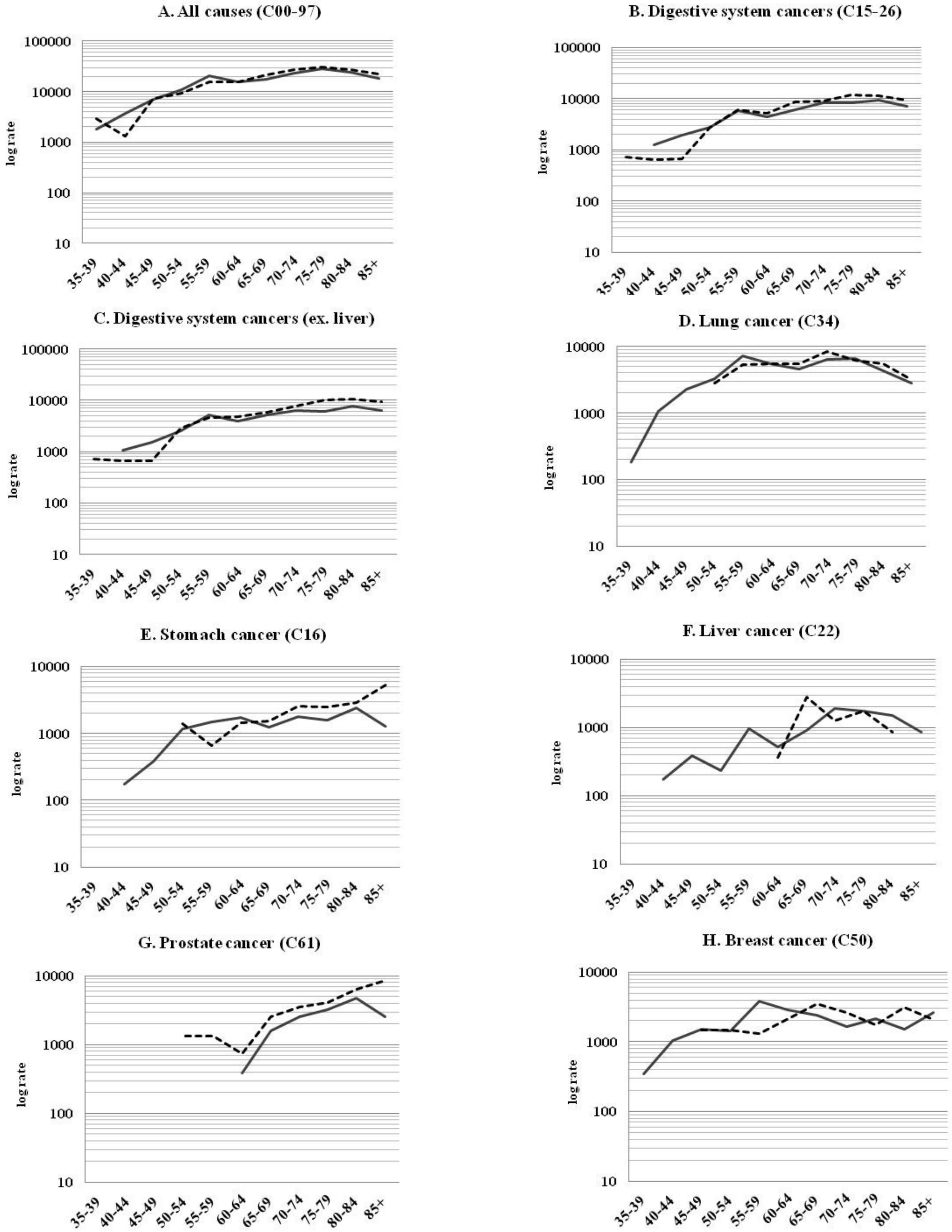
Type of cancer (ICD-10)	Region A (rural) SDR	Region B (urban) SDR	Rate ratio	95%CI
All types (C00–97)	183.4	174.2	1.05	0.91–1.18
Stomach (C16)	18.3	13.3	1.38	0.95–2.00
Colorectal (C18–20)	21.2	16.4	1.31	0.92–1.81
Pancreatic (C25)	10.6	7.8	1.36	0.82–2.26
Liver (C22)	7.0	9.4	0.78	0.47–1.19
Total cancers of the digestive system (C15–26)	66.5	56.0	1.19	0.99–1.43
Total cancers of the digestive system (excl. liver)	57.9	46.3	1.25	1.02–1.54*
Bladder (C67)	6.6	5.9	1.17	0.63–2.00
Kidney (C64)	2.0	3.8	0.50	0.22–1.24
Lung (C34)	42.4	44.3	0.95	0.84–1.09
Brain (C71)	8.1	6.3	1.27	0.93–1.74
Lymphatic/hematopoietic (C81–96)	12.4	10.4	1.20	0.95–1.52
Prostate (C61)	28.1	15.1	1.86	1.10–3.14*
Breast (C50)	22.6	21.3	1.10	0.67–1.68
Endometrial (C54)	4.1	8.1	0.50	0.21–1.18
Ovary (C56)	11.8	10.2	1.16	0.60–2.23

* Statistically significant at $p<0.05$
CI, confidence interval. ICD-10, WHO's *International Classification of Diseases*, 10th edn. SDR, age-standardized death ratio

Table 3: Sex-specific age-standardized cancer mortality

Type of cancer (ICD-10)	Rural SDR			Urban SDR			Rate ratio (95%CI)		
	Both	Male	Female	Both	Male	Female	Both	Male	Female
All types (C00–97)	183.4	267.6	122.0	174.2	240.0	124.1	1.05 (0.94–1.18)	1.11 (0.97–1.28)	0.98 (0.82–1.18)
Stomach (C16)	18.3	27.7	11.7	13.3	19.0	8.9	1.38 (0.95–2.00)	1.46 (0.91–2.34)	1.31 (0.69–2.49)
Colorectal (C18–20)	21.2	26.1	17.3	16.4	21.4	13.4	1.31 (0.92–1.81)	1.22 (0.78–1.91)	1.30 (0.78–2.16)
Pancreas (C25)	10.6	15.7	6.2	7.8	9.6	6.3	1.36 (0.82–2.26)	1.63 (0.84–3.17)	0.97(0.44–2.13)
Total digestive system (C15–26)	66.5	94.1	43.5	56.0	76.9	40.3	1.18 (0.99–1.43)	1.22 (0.96–1.56)	1.08 (0.80–1.45)
Digestive system (excl. liver)	57.9	77.3	41.7	46.3	61.0	35.9	1.25 (1.02–1.54)*	1.27 (0.97–1.67)	1.16 (0.85–1.19)
Total lymphatic/hematopoietic (C81–96)	12.4	15.5	9.6	10.4	10.3	10.3	1.20 (0.95–1.52)	1.51 (0.77–2.94)	0.93 (0.5–1.73)
Lung (C34)	42.4	82.4	10.9	44.3	81.5	14.6	0.96 (0.84–1.09)	1.01 (0.79–1.29)	0.74 (0.44–1.25)

* Statistically significant at $p<0.05$
CI, confidence interval. ICD-10, WHO's *International Classification of Diseases*, 10th edn. SDR, age-standardized death ratio



Grey line, urban. Dashed line, rural

Figure 1: Age-standardized cancer mortality (semi-logarithmic scale).

Discussion

Main findings of this study

This study has generated some interesting insight into cancer mortality with respect to rural–urban geographic reference in north-eastern Greece. Notably, the burden for prostate cancer in rural males was significantly higher when compared to their urban counterparts. Moreover, the incidence of stomach cancer in rural areas was significantly elevated in the older age groups (>65 years), indicating a historical discrepancy between the two regions. In contrast, there was a complete absence of liver and lung cancer cases in younger cohorts from rural areas, which can be attributed to structural differences in the population.

Discussion in light of the literature

Health disparities have been observed between rural and urban regions around the world. Several risk factors have been described as potential drivers of this epidemiological polarization. Access to health care, including distance from medical facilities, physician-to-population ratio, availability of cancer detection technologies and screening methods, constitute some of the most important aspects associated with social deprivation and rurality[25-27]. Limited financial resources and economic factors tend to augment these disparities even further. Moreover, the availability of public versus private medical centers and public health insurance coverage costs appears to be critical factors[28].

Health promotion and education are often trivial in rural populations. Absence of disease control and prevention can lead to increased incidence and mortality. Behavioral factors such as smoking, diet and alcohol consumption may alter individual outcomes, although cultural or religious beliefs may be equally important[29]. Higher levels of stoicism and fatalism have been observed among rural populations, arising from the denial of presenting symptoms and the fear of stigmatization[30]. This may result in increased time to diagnosis, which ultimately leads to heavier tumor burden and worse treatment compliance.

This can be best exemplified in the case of prostate cancer. Prostate cancer typically develops slowly and the tumor may be preceded by dysplastic lesions for many years or even decades. Small and localized prostate neoplasia can thus remain unrecognized for many years before progressing to a clinically significant state. In many autopsies prostate cancers are found incidentally, suggesting that prostate hyperplasia is an inevitable feature of male physiology that comes with advanced age[19]. On the other hand, the introduction of PSA testing to detect prostate cancer has shifted the spectrum of diagnosed cancers from undifferentiated to moderately differentiated tumors (Gleason sum scores 5–7)[31]. Moreover, PSA screening has altered the age distribution of prostate cancer cases in many developed countries. In Germany, the mean age at diagnosis has declined from 73 years in 1980 to 69 years in 2006[32]. The efficacy of the test has raised serious concerns, leading to suggestions for more selective use in high-risk groups only[33]. Nevertheless, early diagnosis of prostate cancer remains the best option as for all cancer types. In fact, 5-year prostate cancer survival rates are close to 100% for local or regional tumors. Conversely, when distant (stage IV, M1) tumors are considered, 5-year survival rates drop to less than 30%[21].

Implications of this study

In this study, the comparison between rural and urban regions has indicated a clear discrepancy regarding prostate cancer mortality. In rural residents, mortality from this type of malignancy was 1.86 times higher when compared to their urban counterparts. This tendency was observed across all age groups, indicating an effect that is independent of age. Moreover, it suggests that the potential modifying factors are probably resilient to population characteristics and thus not crudely determined. A possible explanation for this phenomenon could be the socioeconomic status of agricultural populations. Lack of health attitudes towards preventive (early) screening and diagnosis, in combination with limited medical resources, including the absence of a specialist urologist/andrologist and diagnostic facilities in the area, may predispose for higher prostate cancer morbidity and mortality[33].

A different picture emerges for cancers of the digestive tract. These are principally associated with stomach, colorectal cancers and pancreatic neoplasia (>85% of cases). Only marginal differences were observed between rural and urban areas. For stomach cancer, a probable cohort effect has been observed. In rural areas, the mortality from this type of malignancy was higher in the older age groups. This finding addresses a cultural aspect of cancer epidemiology. Global trends of stomach cancer have been declining since the 1950s[34]. This is due to the dietary transition brought about by the advances in food preservation, the introduction of refrigerators and the overall improvement in the quality of nutrition. This development has led to a decrease in the consumption of salt-preserved food and cured meat, such as pickled or smoked products, and an increase in the availability of fresh substitutes[35]. Technological and dietary advances have thus caused a gradual decline in stomach cancer incidence and mortality on a global scale[36]. However, the cohort of individuals that are over 65 years of age were born between 1934 and 1943 or earlier. This suggests that they may have been exposed to these risk factors for a longer period compared to their urban counterparts, and this may have contributed to their overall burden in developing this type of malignancy.

Impact of the study: strengths and limitations

A clear distinction is drawn between rural and urban regions as regards cancer mortality in north-eastern Greece. Although this study focuses only in two areas representing a small portion of the total population, it may well serve as a general paradigm. Further research is required to establish a full picture of the epidemiological map and assess temporal trends, to confirm this hypothesis on a wider scale. This will then enable intervention studies to be conducted to mitigate the effects of morbidity and mortality. Health promotion and education towards preventive measures, including the benefits of early screening, must be pursued, along with improved access to medical and diagnostic centers[37,38]. Reversing socioeconomic inequalities is the ultimate goal for supporting the health status of rural populations and this goal should be in line with central government policies aiming at more equal distribution of funds and resources. A constant monitoring of social, environmental and epidemiological parameters is necessary, in order to meet public health indicators and sustain long-term quality of life.

For medical practitioners in the rural sector this poses a true challenge. It is mandatory that appropriate training is provided, given that rural populations face special problems, such as ageing-related morbidity and polypharmacy. Creating the appropriate health culture at the primary (prevention) and secondary (screening) level would be beneficial both for the healthcare system and the local communities. This is best envisaged in programs that take into account performance and deliverance as integral components of the developmental process and economic planning.

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