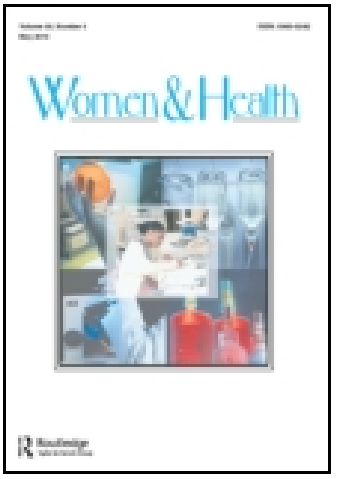

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Joinpoint Regression Analysis of Female Breast Cancer Mortality in Serbia 1991-2010

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Joinpoint Regression Analysis of Female Breast Cancer Mortality in Serbia 1991–2010

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The aim of this descriptive epidemiologic study was to analyze the mortality trends of female breast cancer in Serbia (excluding Kosovo and Metohia) from 1991 to 2010. Average annual percentage of change and the corresponding 95% confidence interval (CI) was computed for trend using linear models assuming a Poisson distribution. The Serbian female population showed an increase in breast cancer mortality continuously from 1991 to 2010 (average annual percentage of change = + 0.9, 95% CI = 0.6–1.1). Breast cancer mortality declined in women aged 30–49 years but increased in women ≥50 years old. Decline in breast cancer mortality in young women was observed during the entire period and was significant in those 35–49 years old. In women 50–54 years old, a significant increase in breast cancer mortality during the period 1991–1997 was followed by significant decrease until 2010.

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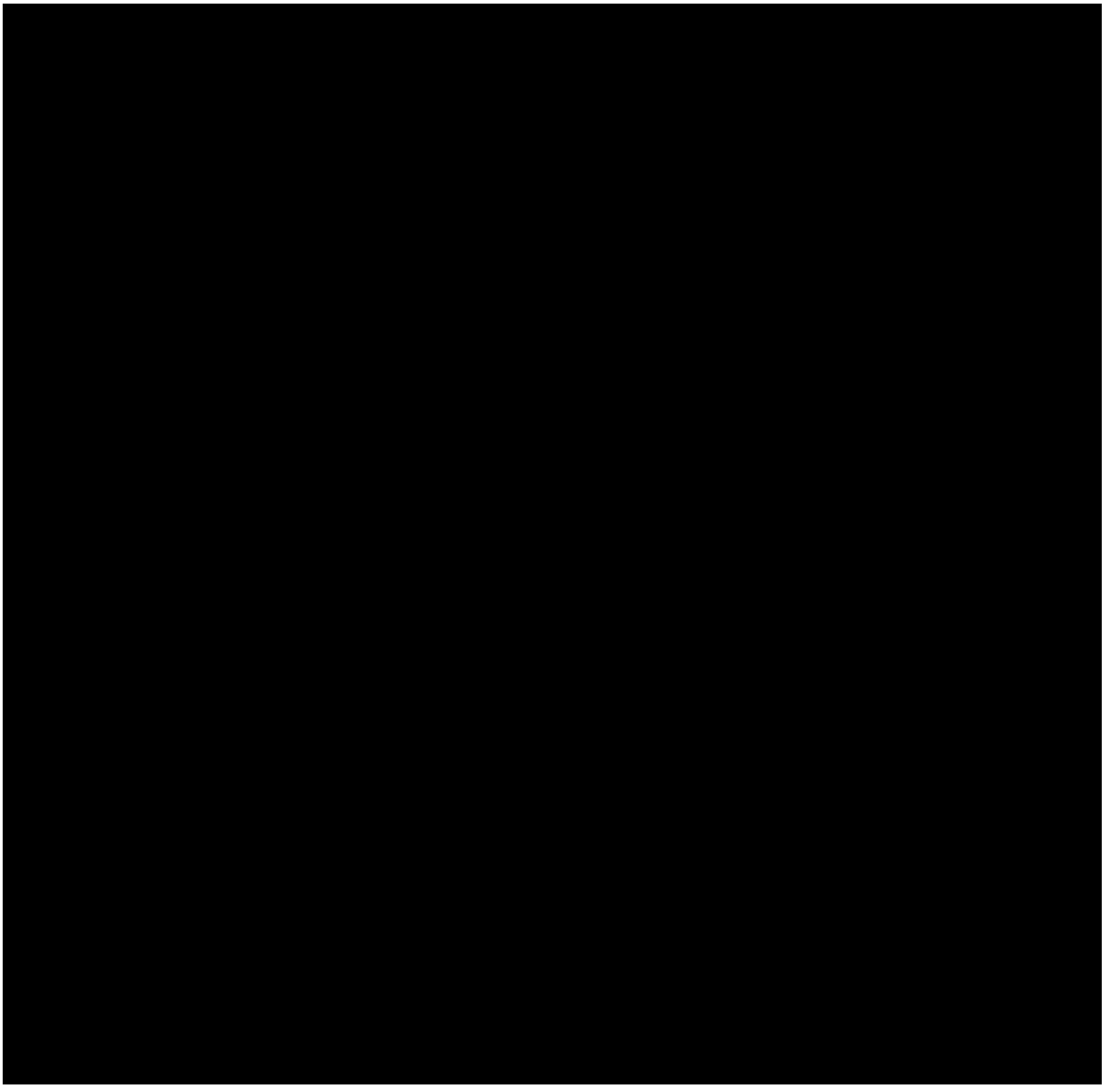
In all older age groups, mortality rates significantly increased during all periods observed. The only exception was among women aged 65–69 years old in whom a small, non-significant decrease in breast cancer mortality was observed in the period 1991–1998, followed by significant increase until 2010. According to a comparability test, breast cancer mortality trends in 30–49, 50–69, and 70+ year age groups differed significantly ($p < 0.01$).

KEYWORDS breast cancer, mortality, trend, joinpoint analysis

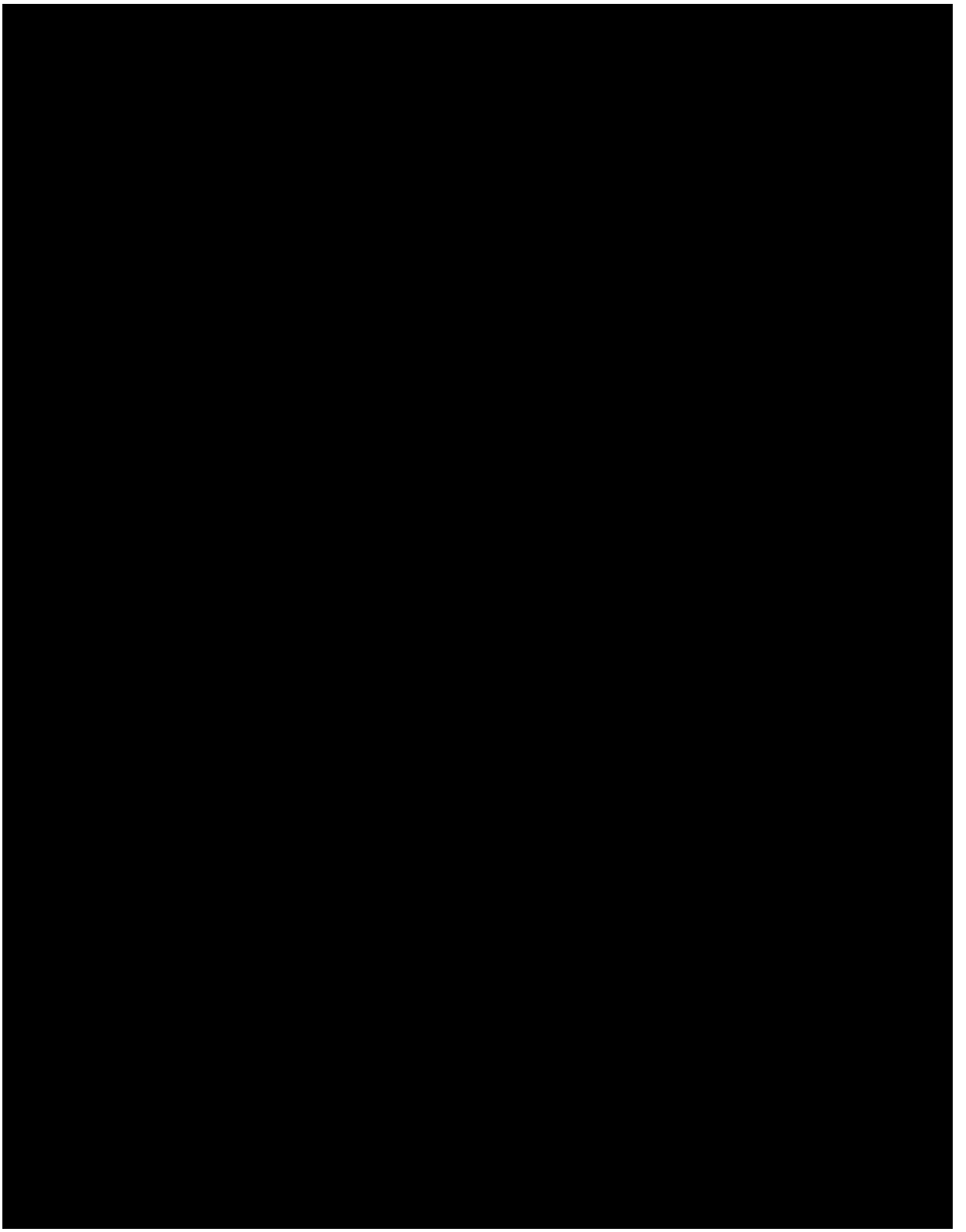


the period 1991–2010. Data on women who died of breast cancer (codes 174 revision 9 and C50 revision 10 of the International Classification of Diseases to classify death, injury, and cause of death) were obtained from the Statistical Office of the Republic of Serbia. Data on the number and composition of the population of the Republic of Serbia by sex and age were obtained from the population censuses in the years 1991 and 2002; for intercensus years, estimates published by the Statistical Office of the Republic of Serbia were used. The age-standardized rates (per 100,000 people) were calculated by direct standardization, using the European Standard Population. Age-specific mortality rates were computed for 5-year age groups. The analysis was conducted on the entire female Serbian population, but the results are not shown for the subgroups aged <30 years, because fewer than 10 cases of breast cancer deaths occurred in each of the quinquennium in any year.

A joinpoint regression analysis was used to determine time segments and the time points in mortality trends for breast cancer. Each joinpoint (if any) marked a significant change in trend, and an annual percentage of change (APC) was computed from each trend using generalized linear models assuming a Poisson distribution. A negative APC indicated a decreasing trend, whereas a positive APC indicated an increasing trend. The analysis began with the minimum number of joinpoints (e.g., 0 joinpoint) and tested whether one or more joinpoints were significant. In the final model, the joinpoint analysis provided average annual percentage change (AAPC); for each AAPC estimate, researchers calculated the corresponding 95% CI. Disparities in age-specific mortality trends were tested by using a comparability test, a procedure proposed by Kim et al. (2004). The main goal of the comparability test is to compare two sets of trend data whose mean functions are represented by joinpoint regression. Each age-specific mortality trend was compared separately with all other age-specific mortality trends, one by one. Two hypotheses were tested: (1) Each of the two age-specific mortality trends being compared were identical, and (2) the two age-specific mortality trends being compared were parallel. Two-sided *p*-values were considered to indicate statistical significance when they were less than 0.05. Joinpoint regression analyses were performed using Joinpoint regression software (Version 3.0), available through the Surveillance Research Program of the U.S. National Cancer Institute. Relationships between breast cancer mortality and time series of different reproductive factors and lifestyle characteristics were examined by Pearson correlation coefficients.

RESULTS

Nearly 29,000 breast cancer deaths occurred in Serbia during the period 1991–2010, with the average annual age-standardized mortality rate (ASR) being 28.73 per 100.000 women (Table 1). Over the 20-year observation



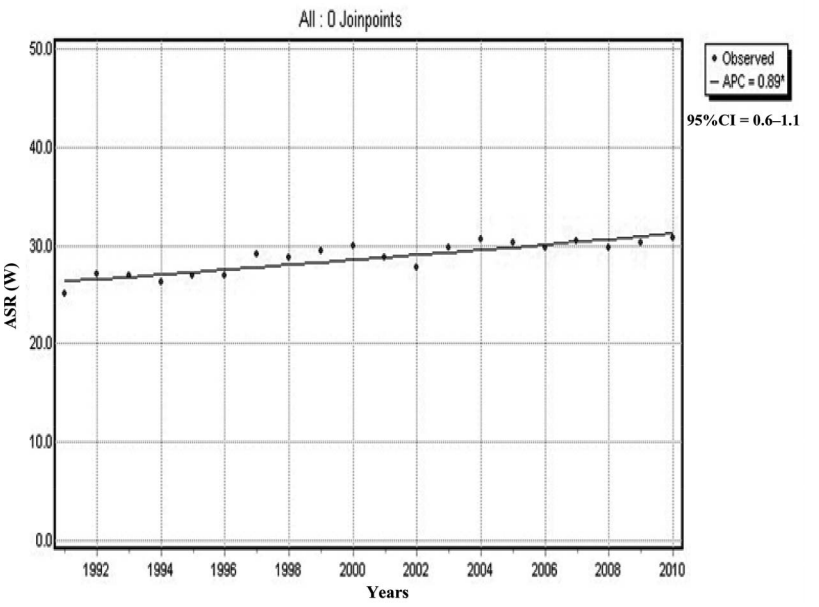


FIGURE 1 Joinpoint regression analysis of female breast cancer mortality rates per 100,000 women in Serbia, excluding the Autonomous Province of Kosovo and Metohia, 1991–2010.

*The APC change is statistically significantly different from 0 (two-sided $p < 0.05$).

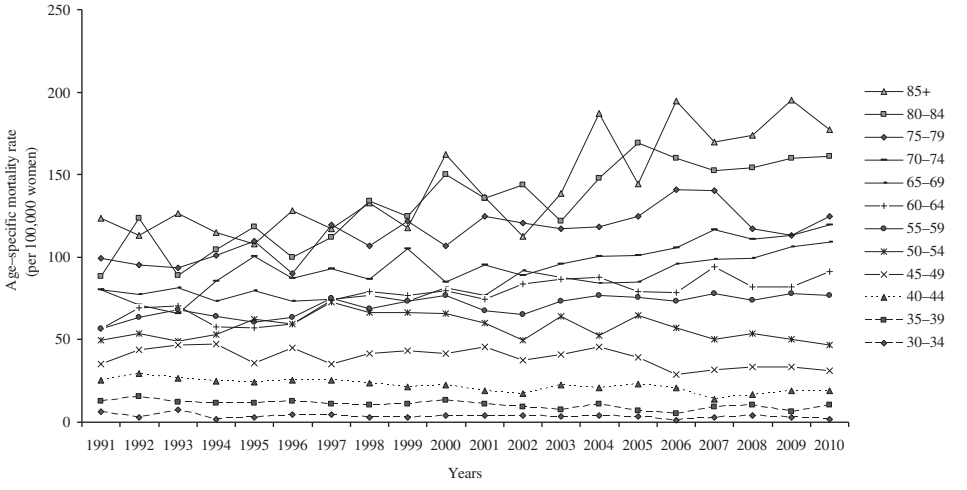
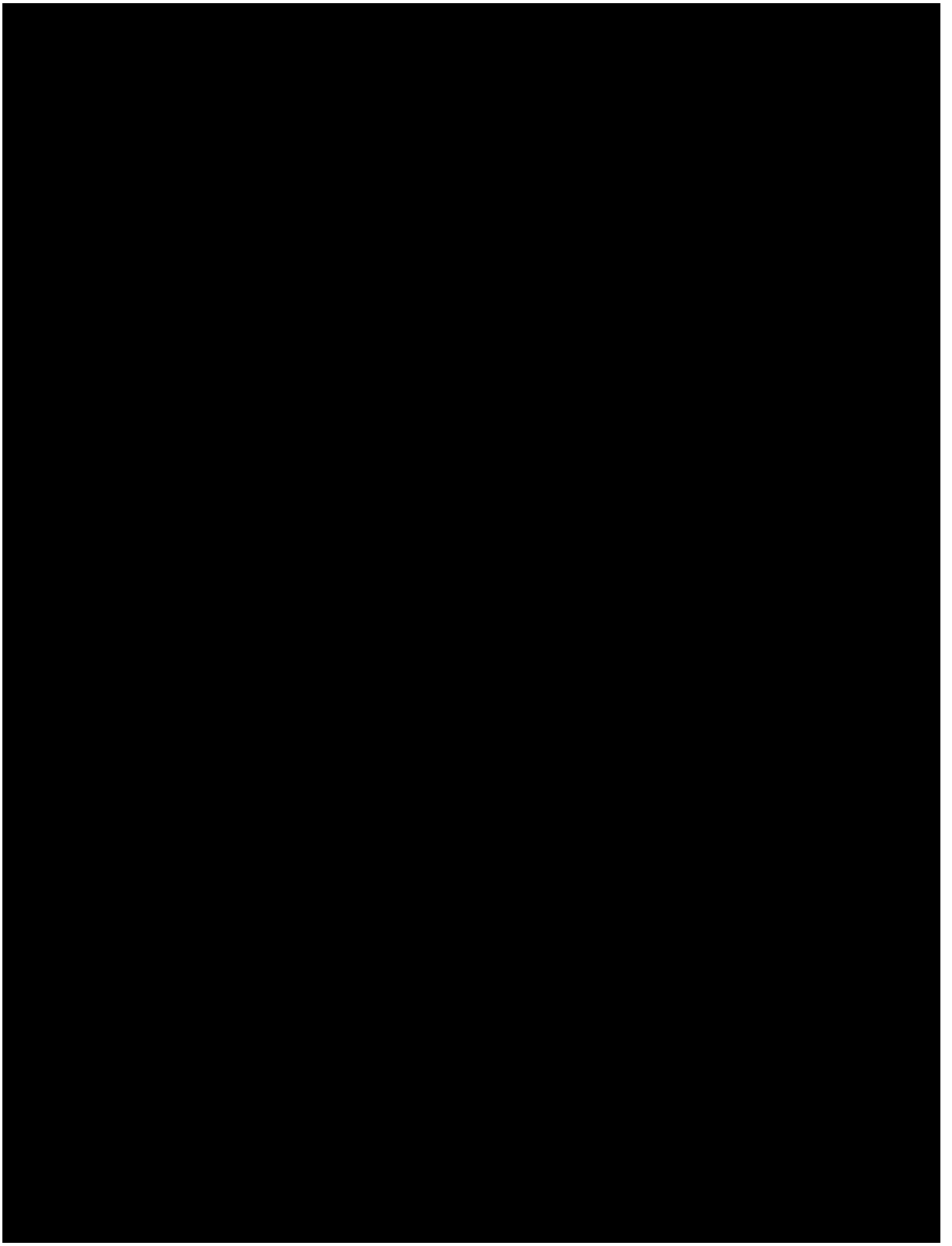


FIGURE 2 Age-specific mortality rates per 100,000 women for female breast cancer in Serbia, excluding The Autonomous Province of Kosovo and Metohia, 1991–2010, by year of death.

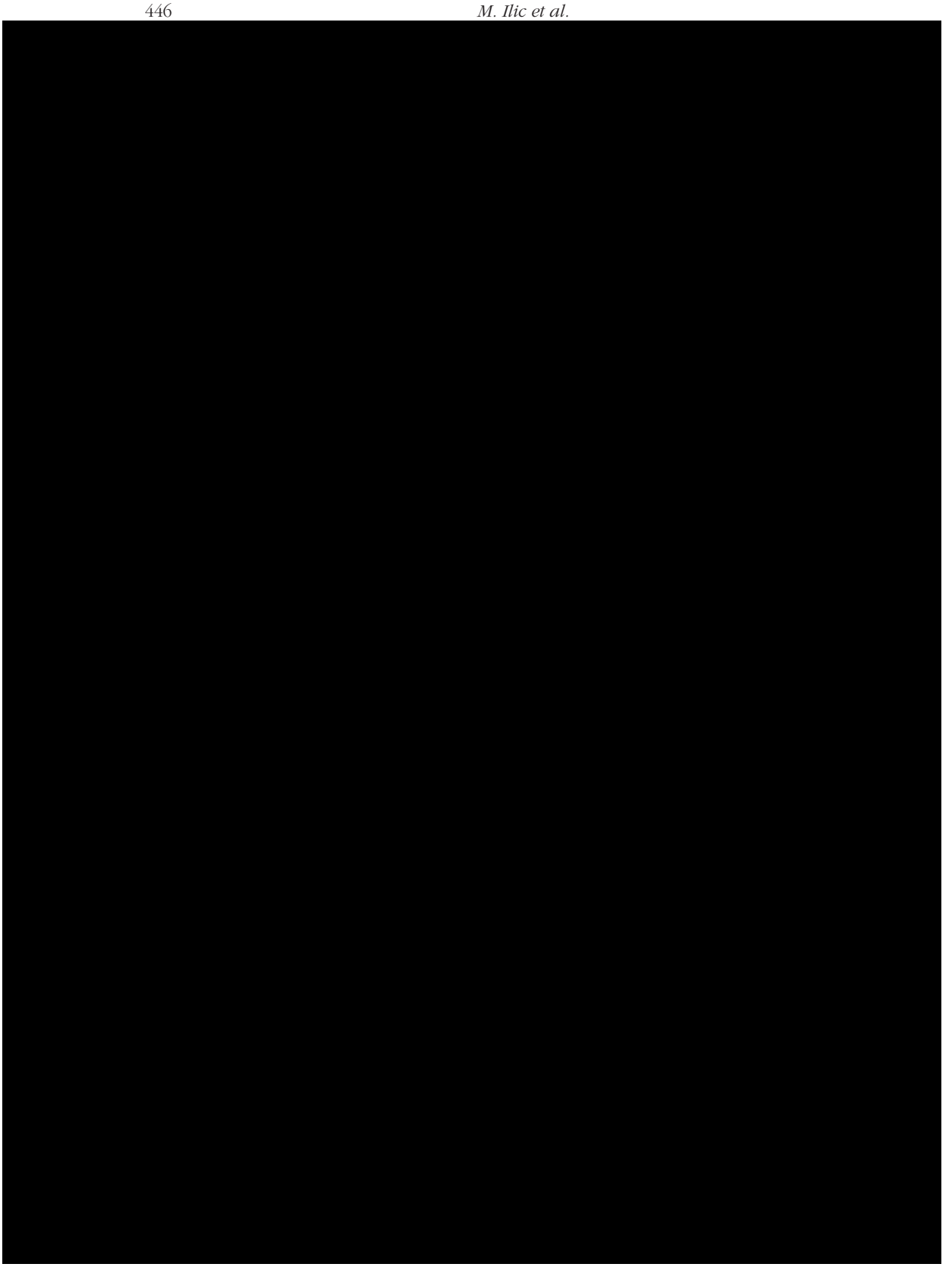


DISCUSSION

Breast cancer mortality rates vary considerably among countries (Ferlay et al., 2010; IARC, 2008; Parkin et al., 2005). The highest standardized death rates in 2008 were recorded in Barbados (29.2 per 100,000 women), Armenia (25.0), Nigeria (22.8), and Belgium (21.0), and the lowest mortality rates (approximately 5 per 100,000) were recorded in Mongolia, China, and Vietnam (Ferlay et al., 2010; IARC, 2008). Countries with intermediate mortality rates (approximately 15 per 100,000 women) were the Russian Federation, United States of America, Poland, Norway, Czech Republic, and Portugal. In the 1991–2010 period, the average annual age-standardized mortality rate of breast cancer in Serbia, excluding the Autonomous Province of Kosovo and Metohia, was 28.73 per 100,000 women. These mortality rates place Serbia among the countries with the highest breast cancer mortality rates in the world.

The decline in breast cancer mortality in all races in the United States was first observed in the late 1980s (Chu et al., 1996; Howlader et al., 2009). From 1975 to 1990, the United States recorded an increasing trend in breast cancer mortality rates of approximately + 0.4% per year, and from 1990 to 2009 a steadily decreasing trend (by –1.8% for 1990–1995 period, –3.2% for 1995–1998 period, –1.9% for 1998–2009 period) (Howlader et al., 2009). Breast cancer mortality has been decreasing appreciably in most Western and Northern European countries from the early 1990s, especially in the United Kingdom (Jemal et al., 2011; Levi et al., 2007; Héry et al., 2008a). However, in most of the countries of Eastern and Central Europe, such as Belarus, Estonia, Latvia, Romania, and Slovakia (Héry et al., 2008a), as well as the Russian Federation (La Vecchia et al., 2010), an increase in breast cancer mortality in women has been recorded. Breast cancer mortality in women has been on the rise since the 1950s in some East Asian countries (Japan, China, Korea, Taiwan), although some declining trends were recorded in Hong Kong and Singapore (Yako-Suketomo & Katanoda, 2011; Shin et al., 2010; Yang et al., 2003).

In addition to being female, age is the most important factor that influences the risk for developing breast cancer (Madigan et al., 1995; McPherson, Steel, & Dixon, 2000). Rates of death from breast cancer also increase with age, with the 50–54 year age group being a surrogate for dividing mortality trends to premenopausal and postmenopausal. While in developed countries breast cancer mortality decreases after menopause (Howlader et al., 2009; Héry et al., 2008a; Shin et al., 2010), in less developed countries mortality rates tend to stabilize after menopause or even to increase (Tyczynski et al., 2004; Héry et al., 2008b). Declines in breast cancer mortality in young women, a flattened trend of mortality in middle-aged (50–54 years), and an increasing trend in elderly have also been observed in Serbia since 1991, as in countries with limited resources.



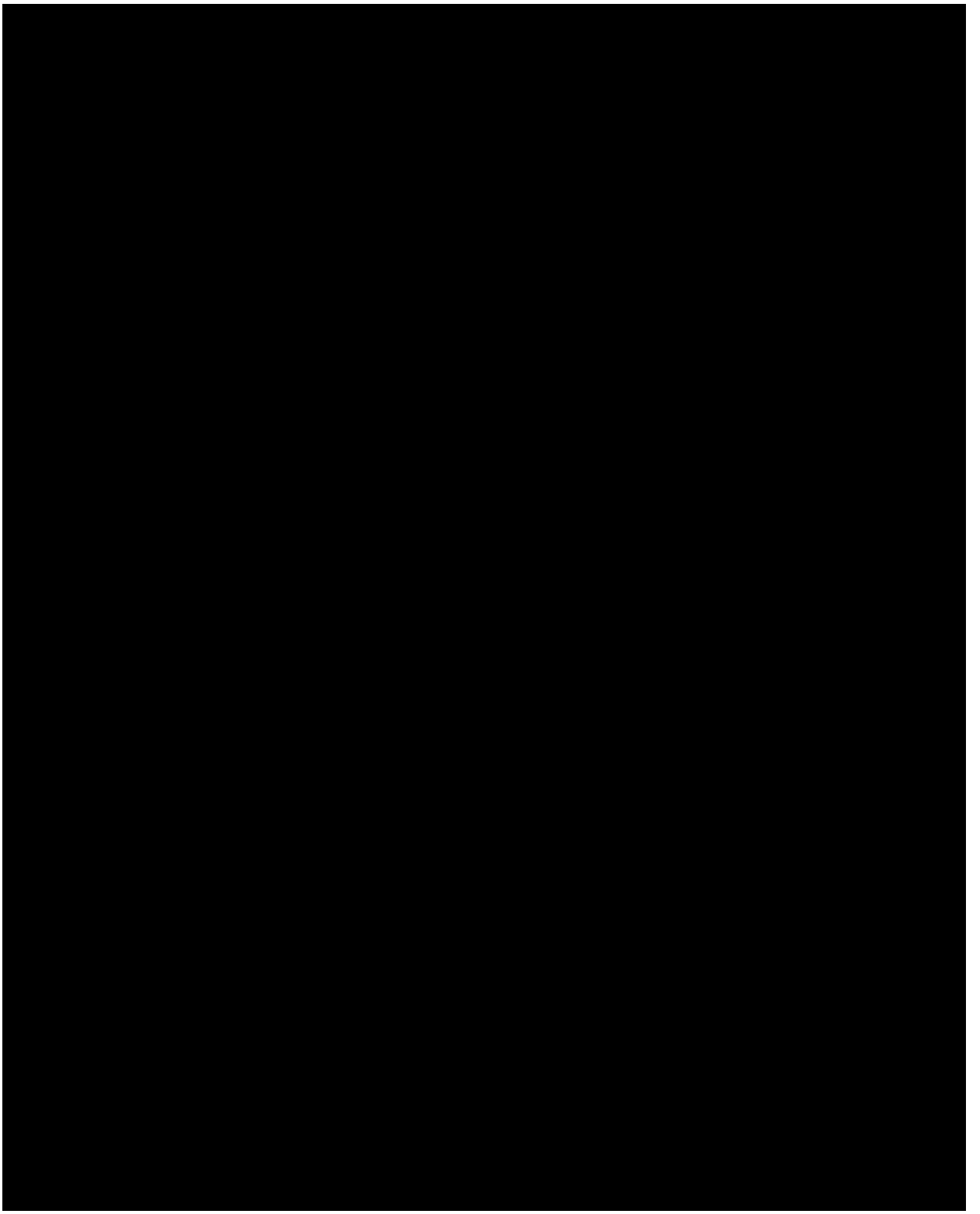
index significantly increased from 26.0 to 26.7 kg/m^2. However, the use of menopausal hormone therapy was very low, less than 1.0% (International Menopause Society, 2013). Out of other possible risk factors, oral contraceptives were used by about every tenth woman (11.6%) aged 20–24 years and by every eighth woman (13.1%) in the age group 45–49 years (Rasevic, 2008); less than 3% of women consumed more than 20g of ethanol per day. Shorter survival of breast cancer patients could have been a consequence of the unfavorable conditions in the health care system during the 1990s and economic problems later. In addition, the proportion of advanced-stage breast cancer at diagnosis is high in Serbia as a result of poor health education. According to data from hospital registers, 35% of women are diagnosed with a localized disease and 49% with regional progression, while 9% already have distant metastases at diagnosis (Jovicevic Bekic & Jovicevic, 2006). As already stated, in Central and Eastern European countries and some countries in Southern Europe (Greece, Slovenia, and Portugal), breast cancer mortality rates decreased from –0.9% to –4.1% per year in women <50 years old and increased from +0.5% to +3.5% per year in women 70 and more years old (Autier et al., 2010). The changes in breast cancer mortality trends in Serbia in the same age groups were –2.0% per year and +2.3% per year, respectively. These age differences may reflect greater breast cancer awareness, better targeting of effective treatments, and response to treatments of younger rather than older women (Eaker et al., 2006; Siebel & Muss, 2005; August, Rea, & Sondak, 1994).

Taking into account changes in reproductive factors and lifestyle and economic problems, it is difficult to predict future trends of breast cancer mortality in Serbia. Implementation of screening mammography is planned for the year 2013. Although the effect of screening on breast cancer mortality is not quite clear, in the population of Serbia in which until now only one-third of patients were diagnosed at early stage of the disease, screening could be beneficial.

While the question remains whether and how much the increasing breast cancer mortality in Serbia could be attributed to the lack of mass screening or appropriate treatment, primary breast cancer prevention as the true goal should not be overlooked.

Strengths and Limitations of the Study

The present study is one of few that have reported data on breast cancer in this part of Europe. The relationship of observed changes in mortality with some of postulated risk factors for breast cancer was also assessed. Of course, as always, the question about the reliability of causes of death reported in national statistics was a limitation. The World Health Organization judged that cause of death data in Serbia were of moderate quality (Mathers et al.,



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