LEVELLING OF CANCER RATES IN THE VERY OLD?

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Introduction

Cancer incidence and mortality increase with age and as life expectancy lengthens; with more people surviving to older ages [1], the number of cancer cases and cancer deaths is projected to increase [2].
It is however unclear how aging contributes to variations in cancer rates. Differences in exposure to risk factors over time may modify cancer risk in birth cohorts, making it difficult to distinguish between whether the oldest old were simply exposed, throughout the lifespan, to fewer risk factors for certain types of cancers [3], being less susceptible to cancer, or whether this result is an artifact due to less intense diagnostic screening or testing in old age [4]. On the other hand, the theory of mutation accumulation should be also considered, i.e. genomic damages accumulate with age during life, increasing the risk of cancer [5, 6].

Objective

To understand the state of cancer burden among the elderly, we described cancer incidence and mortality trends by age and calendar period, with emphasis on individuals 85 and older.

Methods

Mortality data. We retrieved official death certification data from the World Health Organization (WHO) database, available on electronic support (WHOSIS) [7] for all cancers combined and several cancer sites: oral cavity and pharynx (C00-C14), esophagus (C15), stomach (C16), colorectum (C18-C21), liver (C22), pancreas (C25), larynx (C32), lung (C33-C34), breast (C50), uterus (cervix and corpus) (C53 and C54), ovary (C56), prostate (C61), bladder (C67), kidney (C64-C65), non-Hodgkin lymphoma (C81-C90, C96), multiple myeloma (C90), and leukemia (C91-C95). We obtained mortality figures from 2000 through 2014 for 8 major countries worldwide, i.e. those with over 20 million inhabitants and over 95% population death certification coverage [7]: the United States of America (USA), Japan, Australia, the United Kingdom (UK), Germany, France, Italy and Poland. During the calendar period considered, in the WHO database, the 10th Revision of the International Classification of Diseases (ICD) [8] was mainly used (in Italy for 2000-2002 the 9th Revision of the ICD [9] was used, however, since coding differences between various revisions were in general minor, we recoded all cancer sites deaths according to the 10th).
Incidence data. We used Surveillance, Epidemiology, and End Results Program (SEER) 9 Registries [9] to retrieve incidence data on older age groups for the USA. We selected the period 2000-2014 and the same cancer sites considered for mortality data, with some minor differences: we added data on brain and central nervous system tumors (C70-72) for both sexes and thyroid (C73) for men. We did not consider larynx for female because of paucity of data and we were able to distinguish uterine cervix from endometrium.
Population data. We obtained estimates of the resident population for the corresponding calendar periods, based on official censuses, from the WHO and, for the USA, from the Pan American Health Organization (PAHO) databases [10]. Since the main focus of this analysis was on older population groups (85-89, 90-

94, and 95+ years), and since data for these age groups was missing in the WHO and PAHO databases, we retrieved population figures in the older age groups from United Nations Census Bureau database (UN) [11]. Data validity and consistency were cross-checked between the databases. In the cancer incidence analysis, since the SEER 9 Registry does not include population data for 85-89, 90-94, 95+ years age groups, we calculated pseudo-SEER populations using the proportion between UN population and SEER population for the 85+ years age group, stratifying by sex and calendar period. We applied the obtained proportions to the older age groups from the UN population.

Statistical analysis. Using the matrices of certified deaths, cancer cases and resident population, we calculate age-specific mortality and incidence rates for each 5-year age group (from 85 to 95+ years) and the 2000-2014 period. For comparison, we also computed rates for 5-year age groups between 65 and 84. We used joinpoint regression models [12], allowing for up to two joinpoints, to identify age groups in which there were significant changes in mortality trends for the 8 countries and the 17 cancer sites under study plus all cancers combined. We computed the estimated annual percent change (APC) for each of the trends identified by the joinpoint model and the average annual percent change (AAPC) over all age groups considered [13, 14] as a summary measure.

Results

Mortality. Mortality trends over the period 2000-2014 from all cancer combined and for both sexes tended to decrease or flatten at the older age groups (after the age 90-94 for most considered countries and after 85-89 for Poland). In contrast, mortality rates for the USA and France also increased after age 85-89 (Figure 1). Mortality rates were consistently higher in men compared to women.

With the exception of France (0 joinpoints), in men, we identified significant changes in mortality trends at the 80-84 age group and, for the UK and Germany, at 85-89. After the identified joinpoint, the UK showed a tendency to level off (APC of -0.8, non significant), Germany and Poland to decrease (APCs of -5.7 and -12.6, respectively, non significant). AAPCs in men, over all age groups considered, ranged between 21.4 (Germany) and 33.6 (Australia). In women, we identified joinpoints at the 75-79 age group in the USA, and at 85-89 for other countries. Italy showed a tendency to flatten (APC of 0.3), while the UK and Poland to decline (APCs of -1.6 and -12.8, respectively), but none significantly. AAPCs in women ranged between 11.2 (Poland) and 36.1 (Japan).

The highest mortality rates among the very old (85+ years) were for cancers of colorectum, lung, breast, and prostate. For Japan only, stomach cancer mortality was higher than colorectal cancer mortality. Colorectal cancer trends reached a peak at age 90-94 to then decrease for most countries and both sexes, except for the USA and France (rises across all age groups) and Poland (peak at earlier age). In men, lung cancer mortality rates started to decline around the age group 80-84 and 85-89, while in women trends across the various ages were less favourable. Breast cancer mortality increased with age, except for Germany, Italy and Poland, where rates stabilized after age 90-94. Mortality trends for prostate cancer increased across all age groups in the USA, Japan and France, while in the other countries declined after age 90-94 (in Poland after 85-89).

Incidence. Total cancer incidence in men from the USA increased up to the age group 80-84, flattened up to 90-94, to decrease thereafter. In women, after age 80-84, the trend declined.

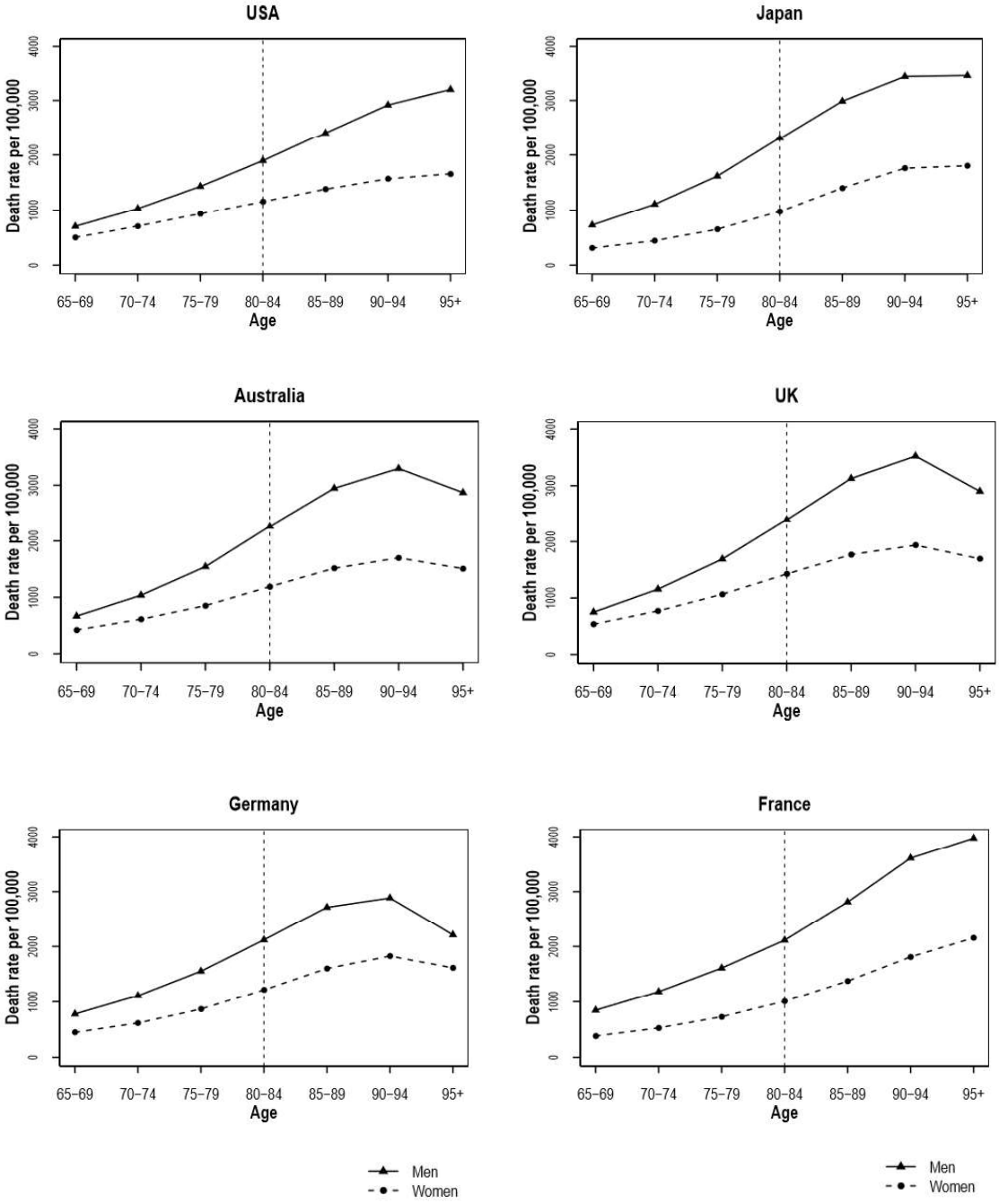
Considering specific cancer sites, the highest incidence rates among US persons aged 85+ were again for cancers of colorectum, lung, breast, and prostate. Colorectal cancer incidence showed declines after the 90-94 age group for men, and for women a plateau between 85-89 and 90-94 age groups, to decline thereafter. Incidence rates for lung cancer increased up to the age 80-84 in men and up to 75-79 in women, to then become favourable. Breast cancer incidence rates in the elderly continued to decline since the age 75-79. Incidence rates for Prostate cancer decreased up to the age 90-94, to then flatten.

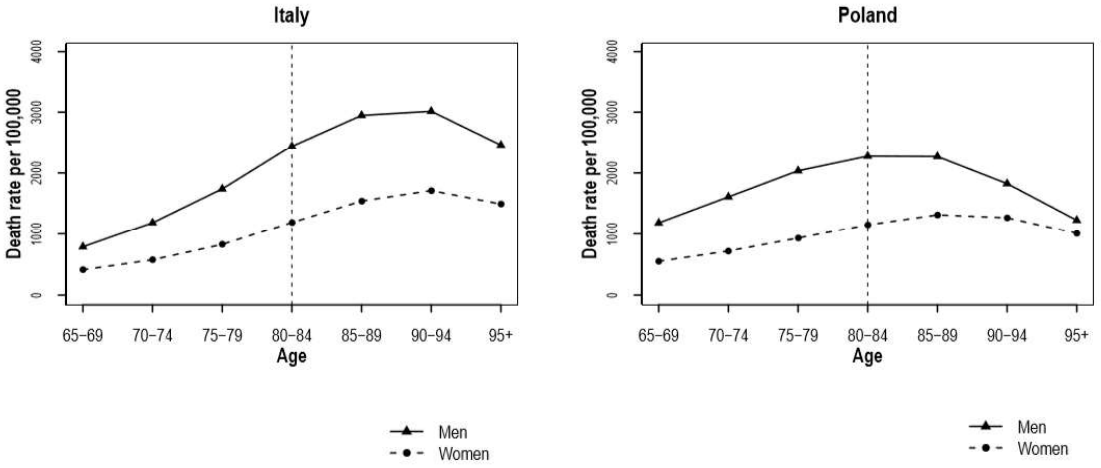
Conclusions

Overall cancer mortality decreased at older age groups, mostly after 90 years of age. Incidence trends showed declines at earlier age compared to those of mortality trends.
Considering specific cancer site, elderly colorectal cancer patients tend to have a more advanced disease stage, they also have more comorbidities and are treated less aggressively compared their younger counterparts. Advanced colorectal cancer often requires major surgery as part of treatment, the comorbidities heavily influence surgical eligibility and potential benefit from other treatment options [15]. This is probably why we found less favorable trends in older age compared to other cancer sites. However, the combination of comorbidity conditions and the avoidance of higher risk therapies, that may cause non-cancer death, could explain the declines observed in the oldest age group.
Lung cancer mortality and incidence rates for the USA have similar trends across age groups, this is due to the low survival for this cancer site. Female smoking patterns reached similarity with those of men worldwide [16], this probably caused the observed differences in trends between the two sexes.
While some studies have proposed that older women may present more aggressive breast cancer or may be at a higher risk due to being outside the screening coverage, others studies have documented that elderly women have a less aggressive disease and a more favourable tumour marker profile [17]. Further, the decreased levels of sex hormones in older adults contributes to a hormonal environment that is less likely to stimulate the growth of breast cancer [18].
The favourable trends in mortality and incidence rates for prostate cancer are probably mainly due to a reduction in overdiagnosis, particularly in the USA (screening was stopped for men over age 75 in 2008 and for all men in 2013) [19].
A paucity of data regarding cancer mortality trends in persons aged 85+ has been noted. Health conditions in the elderly are complex and heterogeneous (comorbidities, multiple drug use, etc.), causing difficulties in cancer care. As a consequence, older people are commonly excluded from clinical trials or aggregated as 85+ years in population-based analyses [20-22].
This work examined cancer mortality and incidence among individuals aged 85 years or more, by major cancer sites and countries using accurate estimates that are based on the quality of national incidence and mortality data of SEER, WHO and PAHO databases [7, 23]. While some studies have found that the population of the very old in the USA is overestimated, leading to underestimated rates for those over 85 years [24, 25], we have utilized validated PAHO/WHO data [26]. Incidence and mortality rates were also stratified by period trends to elucidate trends that may be due to changes in diagnostic criteria and treatment improvements.
However, identifying the underlying cause of death may be challenging in older adults who may present several non-cancer comorbidities; changes in criteria for cancer death diagnosis and inaccuracy in coding and classification likely affect mortality and incidence trends over time. Quantifying the consequences of uncertainties in cancer death certification on observed changes in rates remains difficult. Recent improvements in early diagnosis and cancer death classification have influenced incidence data, but their role on mortality trends is still not entirely clear. Another limitation of this analysis is that we were only able to calculate incidence trends among the very old in the USA, providing a limited scope of incidence trends among those 85+ years. Lastly, to maximize the accuracy of age-specific mortality trends, our study was limited to countries with large populations and 95% population death certification coverage [7].
Therefore, care must be taken not to extrapolate the interpretation of these findings, particularly to low- and middle- income countries with varying access to diagnostic and treatment resources.
This is the first study of mortality in old age that examines both period and cohort specific effects worldwide. Two different processes seem to have been working together in relation to the changes in cancer mortality during the period 2000-2014. Less exposure to risk factors and better cancer prevention, screening and treatment over the period have caused mortality rates to generally decrease.

Cancer incidence and mortality generally increase with age. However, beyond a peak at 80 to 85 years, mortality is likely determined by factors pertaining to lifestyle and risk factor exposure, diagnosis, and treatment that are site specific.

Figure1. *Cancer mortality trends for all cancer combined, in men and women, across 5-year age groups (from 65-69 to 95+ years of age), in 8 major countries worldwide, 2000-2014.*





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