Int J Public Health (2014) 59:341–350
DOI 10.1007/s00038-013-0507-9

ORIGINAL ARTICLE

Innovations in health care and mortality trends from five cancers in seven European countries between 1970 and 2005

Rasmus Hoffmann · Iris Plug · Martin McKee · Bernadette Khoshaba · Ragnar Westerling · Caspar Looman · Gregoire Rey · Eric Jougla · Katrin Lang · Kersti Pärna · Johan P. Mackenbach

Received: 15 March 2013 / Revised: 13 August 2013 / Accepted: 15 August 2013 / Published online: 29 August 2013

Abstract
Objectives Although the contribution of health care to survival from cancer has been studied extensively, much less is known about its contribution to population health. We examine how medical innovations have influenced trends in cause-specific mortality at the national level.
Methods Based on literature reviews, we selected six innovations with proven effectiveness against cervical cancer, Hodgkin's disease, breast cancer, testicular cancer, and leukaemia. With data on the timing of innovations and cause-specific mortality (1970–2005) from seven European countries we identified associations between innovations and favourable changes in mortality.
Results For none of the five specific cancers, sufficient evidence for an association between introduction of innovations and a positive change in mortality could be found. The highest association was found between the introduction of Tamoxifen and breast cancer mortality.
Conclusions The lack of evidence of health care effectiveness may be due to gradual improvements in treatment, to effects limited to certain age groups or cancer subtypes, and to contemporaneous changes in cancer incidence. Research on the impact of health care innovations on population health is limited by unreliable data on their introduction.

Keywords Cancer · Mortality · Health care innovation · Outcome assessment (health care) · Amenable mortality

Electronic supplementary material The online version of this article (doi:10.1007/s00038-013-0507-9) contains supplementary material, which is available to authorized users.

R. Hoffmann (✉) · I. Plug · C. Looman · J. P. Mackenbach
Department of Public Health, Erasmus Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands
e-mail: r.hoffmann@erasmusmc.nl

M. McKee · B. Khoshaba
Department of Health Services Research and Policy, London School of Hygiene and Tropical Medicine, 15–17 Tavistock Place, London, UK

R. Westerling
Department of Public Health and Caring Sciences, Uppsala University, P.O. Box 564, 751 22 Uppsala, Sweden

G. Rey · E. Jougla
CépiDc INSERM, 44 Chemin de Ronde, 78116 Le Kremlin-Bicêtre, France

K. Lang · K. Pärna
Department of Public Health, University of Tartu, Ravila 19, 50411 Tartu, Estonia

Introduction

Cancer is a major cause of death in the European Union, killing about 1.9 million persons every year (Ferlay et al. 2010). Age-standardised death rates have been falling, from just over 200/100,000 in 1990 to 170/100,000 in 2010 (WHO Health for All Database). However, this overall trend conceals a more complex picture, with marked differences by cancer site (Leon 2011). These are driven by changes in incidence (themselves representing historic changes in risk factors, such as declining rates of smoking for males) but also by improvements in early detection and treatment. Yet, in the current climate of austerity, when expenditure on health care is coming under scrutiny (McKee et al. 2012), it is not clear how much health care has contributed to this improvement (Meerding et al. 2007). Although there is a large body of research on the contribution of specific treatments to survival, there is

much less evidence on the impact on mortality at a population level (Carr-Hill et al. 1987; Charlton and Velez 1986; Mackenbach et al. 1988).

This has led to calls for research on the extent to which innovations in health care have actually contributed to population health (Mackenbach et al. 1990; Westerling 1996), especially in the light of questions about the effectiveness of programmes such as mammographic screening (Gotzsche et al. 2012). This study seeks to determine whether the introduction of selected health care innovations coincided with a favourable change in the trend of mortality from five cancers in seven European countries. A brief review of health care interventions for which effectiveness was shown in clinical studies is given below. Selected references for the timing of each innovation in each country are offered as Online Resource.

Breast cancer

A modelling study from the USA estimated that screening reduced breast cancer mortality by 12.4 % and treatment reduced it by 14.6 % (Mandelblatt et al. 2006). The evidence that mammographic screening is effective in saving lives (Duffy et al. 2010) has been disputed (Autier et al. 2011; Gotzsche et al. 2012) but a recent report from the UK concluded that it was effective (Marmot et al. 2012). Second, Tamoxifen has been shown to be effective in prolonging survival, especially in women with oestrogen receptor-positive disease (McGuire 1978). Although the benefits of screening are still controversial, it is likely that the observed reductions in population level mortality reflected the combined effect of both screening and adjuvant therapy. We chose screening with mammography and treatment with Tamoxifen as key interventions.

Cervical cancer

A long-term decline in cervical cancer mortality has continued over the last decade, widely attributed to the wider adoption of organised screening programmes in western and northern Europe (La Vecchia et al. 2010). This view has been supported by the observed clear association between coverage and comprehensiveness of screening programmes and mortality reduction across countries (Office of Population Censuses and Surveys 1975/1982) (Laara et al. 1987). Survival from cervical cancer has also been improving in the past decades (de Kok et al. 2011). As key intervention we chose cervical screening (Department of Health and Social Security 1988). It is difficult to ascertain how much of the observed decline in mortality can be attributed to screening because of changing incidence. Nonetheless, where population-based screening programmes exist, a substantial reduction in mortality has been achieved. There is little evidence to suggest that new treatments for invasive cervical cancer treatment are having a significant effect at a population level (Tewari and Monk 2009).

Testicular cancer

Testicular cancer mortality has declined in the EU from 0.47 in 1990–1994 to 0.35 per 100,000 in 2000–2004 (La Vecchia et al. 2010). Relative survival has risen from 96 % (1 year after diagnosis) and 91 % (5 years after diagnosis) in 1986–1990 to 98 % (1 year) and 97 % (5 years) in 1996–1999 (Nur et al. 2008). These improvements have resulted from advances in combination chemotherapy. Although the combination of developments at the time it was being introduced makes it difficult to quantify its effect on mortality with certainty, we chose the introduction of Cisplatin to be the key intervention against testicular cancer.

Hodgkin's disease

Age-adjusted mortality rates from Hodgkin's disease in 19 European countries fell by 70–80 % between 1965–1969 and 1995–1998 (Levi et al. 2002). Five-year relative survival rate for Hodgkin's disease between 1940 and 1964 improved from 24 to 41 % (Frei and Gehan 1971). Since the 1940s, when combined chemo- and radiotherapy was introduced, and when 5-year relative survival rates of 40 % were already being achieved with rudimentary regimes (Pederson and Mukherjee 2011), a series of advances in treatment have approximately doubled the survival rate (Janssen-Heijnen et al. 2005). The key intervention in the period 1970–2005 is high dose therapy combined with peripheral blood stem cell transplantation (Robinson et al. 2001).

Leukaemia

Mortality from acute non-lymphocytic leukaemia (ANLL) and chronic myeloid leukaemia (CML) fell by 7 % per year and 5 % per year, respectively (own analysis for UK). Despite variations in survival in relation to age, country, histological subtype and period of diagnosis overall 5-year relative survival was 37 % for ANLL and 44 % for CML (Dama et al. 2006). We chose as key intervention the improved treatment of disease process and complications combined with the inclusion of younger patients.

Methods

Mortality data

We studied Estonia, France, West Germany, The Netherlands, Spain, Sweden and the United Kingdom as examples

of different European health systems. For these countries, cause-specific mortality data covering the whole population and covering the period from 1970 to the latest available year (2005, 2006 or 2007) by 5-year age groups and gender were provided by the national statistical offices. Data on mortality from Hodgkin's disease could not be used in Estonia because the Soviet coding system was used in the early part of the period. An overview of the number of deaths and the exact ICD coding is given in Table 1.

Selection of relevant innovations

To define a distinct clinical innovation of proven effectiveness introduced between 1970 and 2005, a series of systematic literature reviews was undertaken, which sought two types of evidence on the effectiveness of the innovation on mortality: first, well-conducted observational studies documenting a decline in mortality that could plausibly be attributed to the intervention and second, randomised controlled trials showing a decline of 30 % or more. Applying these criteria yielded six interventions related to the chosen conditions (Table 2).

Timing of introduction of innovations

Country-specific information was obtained on the year of introduction and the process of diffusion for six health care innovations related to the five causes of death. We developed a questionnaire in which national experts were asked to identify sources of information about the introduction of innovations and to provide information from a wide range of data sources, such as national guidelines, committee reports, scientific publications, expert interviews, and data on registration and on introduction and sales of pharmaceuticals (the questionnaire can be found in our project report at http://amiehs.lshtm.ac.uk). Furthermore, a literature review was performed for each innovation and country (a selection of references to the introduction of each innovation for each country is offered as Online Resource). This was integrated within a theoretical framework of "diffusion of innovation" (Ryan and Gross 1943), further developed by Rogers (2002). Then we derived periods of 4–10 years where a decline in cause-specific mortality could be expected, taking into account a time lag for a sufficient diffusion of the innovation and one for the impact on mortality on the patient level. We looked for both very early indicators of early adopters introducing the method and indicators of a continued diffusion of the method. We used specific criteria for defining hypothesis on the time period when we would expect a favourable shift in mortality trends due to the introduction of the innovation.

Criteria 1

The first documented year of introduction of the innovation in a specific country was used to define the year of the start of diffusion. The start of first clinical trials or studies, available sales statistics from the introduction period or evaluation reports describing the introduction of the innovation were accepted as data on the start of diffusion. When no data was available, the year of registration or national decision was used.

Criteria 2

To define a hypothesis of expected influence on the mortality trends we also need data indicating a continued diffusion of the innovation. This was indicated by further clinical trials, evaluation reports, guidelines, national programmes and sales statistics. A maximum period of 10 years was used as implementation period.

The choice of time period was limited to the study period 1970–2005, i.e. when the main part of the expected period was found to be outside this study period no time period was defined. Further criteria details for specific situations have been published elsewhere (Plug et al.

Table 1 Number of deaths in the study period by cause (ICD-9 and ICD-10), country and gender

	Breast cancer (174;C50)	Cervical cancer (180;C53)	Testicular cancer (186;C62)	Hodgkin's disease (201;C81)		Leukaemia (204–208;C91–C95)	
	Women	Women	Men	Men	Women	Men	Women
Estonia (1970–2005)	7,201	3,063	271	1,151	1,010	1,782	1,765
France (1970–2005)	344,901	29,941	5,814	9357	6,110	72652	60,882
W-Germany (1970–2005)	490,979	71,797	9,788	1,4011	11,540	83,225	79,244
Netherlands (1970–2007)	116,825	11,377	1,611	2,829	1,968	19,623	16,258
Spain (1970–2007)	176,423	15,892	1,799	6,978	4,440	39,723	31,368
Sweden (1970–2006)	547,14	77,90	777	1,634	1,151	13,380	11,092
UK (1970–2006)	452,158	62,330	5,366	1,0150	6,955	67,519	56,434

Table 2 Overview of periods of expected mortality decline based on innovations in health care, and favourable changes in mortality matching these periods

Cause of death	Breast cancer		Cervical cancer	Testicular cancer	Hodgkin's disease	Leukaemia
Innovation	Mammography	Tamoxifen	Introduction cervical screening	Cisplatin	High dose therapy and peripheral blood stem cell transplantation	Improved treatment (management of the disease process and its complications for younger patients)
Estonia						
Period	Nhd	1992–2001	2003–	1995–2003	NA	NA
Match		2000 (F)				
France						
Period	1989–1996	1981–1988	Nhd	1977–1984	1992–1999	1980–1987
Match	1989 (F)					1985(M)/1981(F)
W-Germany						
Period	2001–2005	1981–1988	1971–1978	1973–1980	1988–1995	1978–1985
Match		1986 (F)	1973 (F)	1977 (M)	1990 (F)	1978 (F)
Netherlands						
Period	1975–1982	1981–1988	1980–1987	1976–1983	1994–2001	1972–1979
Match						
Spain						
Period	1992–1999	1988–1995	Nhd	1981–1988	1992–1999	1978–1985
Match	1993 (F)	1993 (F)			1993 (F)	
Sweden						
Period	1976–1983	1976–1985	1970–1977	1981–1988	1985–1992	1975–1982
Match						1980(M)/1977(F)
UK						
Period	1979–1986	1976–1983	1985–1992	1976–1983	1999–	1977–1984
Match			1988 (F)	1976 (M)	2002 (M)	

NA not available, because sufficient information on the introduction of the innovation was not available

F female; *M* male, *Nhd* no hypothesis defined

2011). It should be noted that we apply an ecological design without information on individual treatment or individual mortality outcome.

Description of mortality trends

To identify significant changes in mortality that might be associated with health care, mortality trends based on annual data need to be simplified to see only significant changes of the trend. We used joinpoint models based on Poisson linear spline regression (using the software R) to identify "knots" in the national gender specific mortality trend that mark the years in which a significant change in mortality occurred (Otto et al. 2003). This method is especially apt for the analysis of time trends because it uses dummies in the regression model that equal 1 in a certain period and 0 otherwise. Periods differ in their slopes and the lengths of the periods are estimated in an iterative process until the optimal fit to the mortality trend is found. For our analysis, we concentrated on "favourable" changes in mortality which means either a change from mortality increase to decrease, a change towards a slower increase, or a change towards a faster decrease. Besides the timing of the knots this analysis also produced the per cent annual change for each of the periods between the knots.

Within the period between 1970 and 2005 several ICD revisions were used. We developed a method to calculate correction factors to adjust for the influence of changes in ICD coding on the mortality trends (Rey et al. 2011) based on the Polydect method (Zhang et al. 2009). To identify any possible cohort effect on mortality trends an age–period–cohort (APC) analysis was performed. As these analyses did not identify cohort effects, we retained the original analyses. Based on the spline regression, we produced figures with the mortality trend age-standardised to the European standard population. In a first set of analyses no age limit was used, then we repeated the analysis for the age range 0–74.

Association between mortality trends and innovations in health care

We established whether a favourable change in mortality ("knot") occurred during the period of expected mortality decline. If a knot falls within this period, this was defined as a "match", suggesting that the innovation may have had a positive impact on mortality. To conclude that a certain number of matches provide sufficient evidence for an association we followed two approaches:

1. Likelihood test: for each cause of death, we calculated the likelihood to find the observed number of matches under the assumption that the knots are randomly distributed in time. From this expected probability we derived the expected number of matches, compared this to the observed number of matches and reported the statistical significance of this difference. Because of problems with the reliability of the available data on the introduction of innovations, we performed a sensitivity analysis that divided the innovation data into two groups of more and less reliability and repeated the statistical test for both groups.
2. Count of matches by condition on the country-level: To reveal which of the causes of death was responsive to innovations in health care, we counted the countries that show a match for a condition. For cancers that can occur in both sexes, we weighted countries where only one showed the association by 0.5. If more than half of all countries with available data show the association, we took this as evidence for an impact of the innovation. A detailed description of our study methods is published elsewhere (Hoffmann et al. 2012).

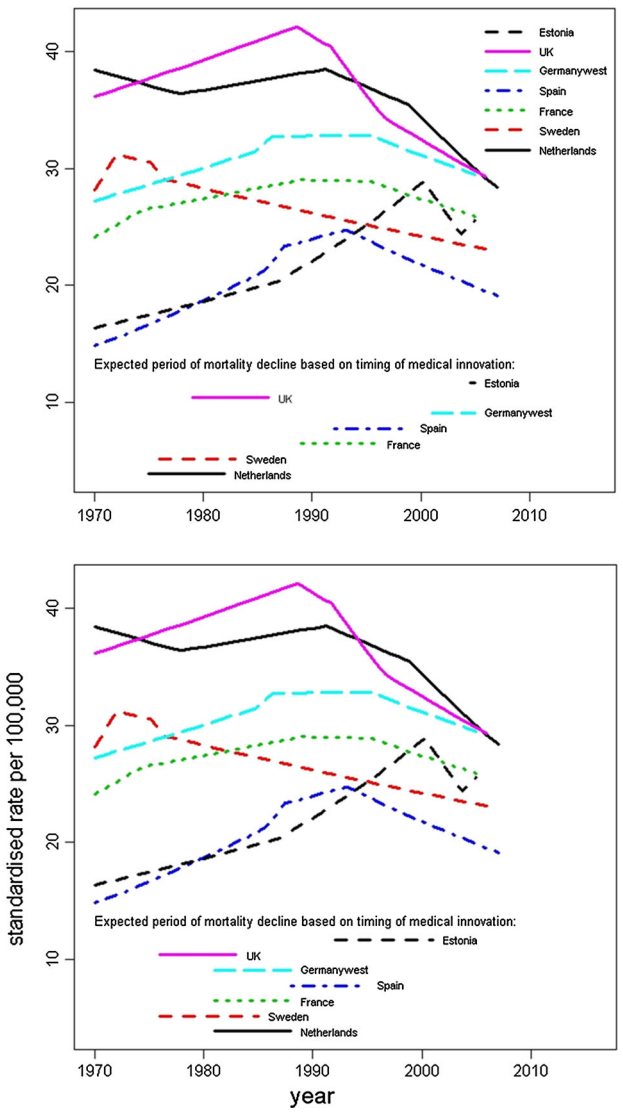

Fig. 1 Estimated standardised all-age mortality trend from breast cancer for women (1970–2005) and expected period of mortality decline based on introduction of mammography (*upper panel*) and Tamoxifen (*lower panel*)

Results

Table 2 gives an overview of the periods of expected mortality decline for each innovation. If a knot falls within this period, we present the year of this match in the row below the period.

Figures 1, 2, 3, 4, and 5 show the mortality trends of the five causes of death for all countries. The straight horizontal lines below the mortality graphs indicate the period of mortality decline that can be expected as a consequence of the specific innovation in health care. Mortality trends across countries for breast cancer (Fig. 1) show a clear inverse U-shaped pattern with turning points from increasing to decreasing mortality concentrated around the year 1990. However, there are countries having this turning point much earlier, such as Sweden in the early 1970s, or much later, such as Estonia in 2000. For mortality from cervical cancer (Fig. 2), we see a steep continuous decline in all countries, except for Spain that experienced an increase levelling off after 1989. All countries show declining mortality from testicular cancer (Fig. 3) with decreases starting to flatten in the 1990s. In Spain the decline is preceded by a sharp increase. In all countries, mortality from Hodgkin's disease (Fig. 4) has decreased throughout the study period with several fluctuations of this decline. For example, in Germany the decline is preceded by a short period of increasing mortality before 1980. Mortality trends for leukaemia (Fig. 5) show convergence between countries between 1970 and 1990 with some improving countries (Sweden, Netherlands) but also increasing mortality, e.g. in Spain. After 1990 there is mostly parallel decline between countries for males but

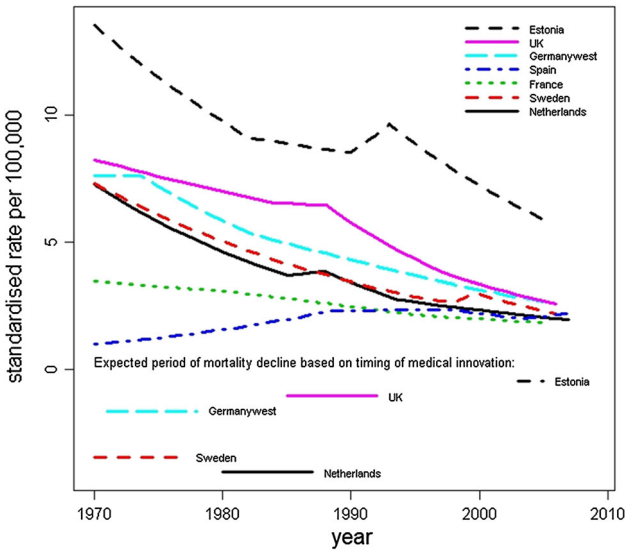

Fig. 2 Estimated standardised all-age mortality trend from cervical cancer for women (1970–2005) and expected period of mortality decline based on timing of introduction cervical screening

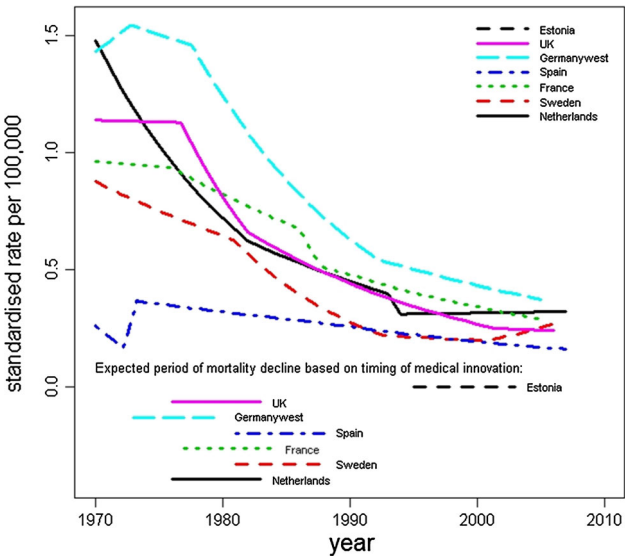

Fig. 3 Estimated standardised all-age mortality trend from testicular cancer for men (1970–2005) and expected period of mortality decline based on introduction of Cisplatin

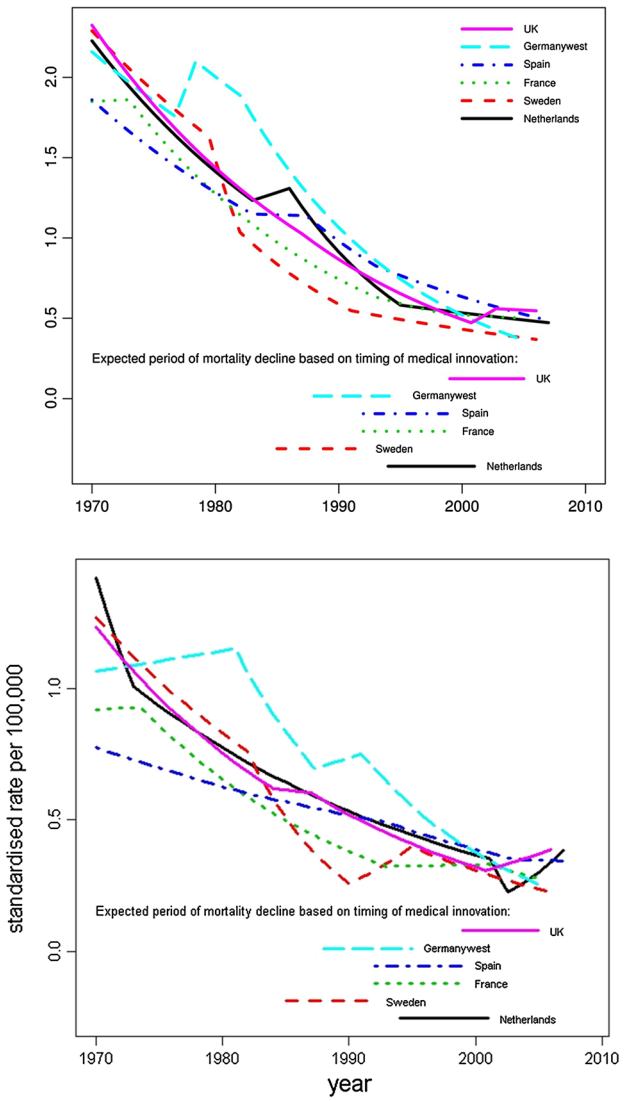

Fig. 4 Estimated standardised all-age mortality trend from Hodgkin's disease (1970–2005) for men (*upper panel*) and women (*lower panel*) and expected period of mortality decline based on timing of introduction of high dose therapy/peripheral stem cell transplantation note: after discussion of the Estonian mortality data with national experts we decided to exclude Estonia from the study of Hodgkin's disease, because the mortality data was unreliable

mortality is increasing for females in Estonia. Overall, mortality from the different cancers shows a declining trend, with some exceptions. We also see convergence of mortality between countries.

The upper part of Table 3 shows the results of the likelihood test for the randomness of the occurrence of matches. The assumption of a random distribution cannot be rejected for any of the five causes of death because the difference between the expected and the observed probability of a match is always non-significant. It should be mentioned that the statistical power of this test by cause of death is low and so is the chance of a significant difference. We also performed a sensitivity analysis that grouped the data on the timing of innovation into data that allowed a direct indication of the time period and data only allowing for an indirect indication. Direct indication means that we have an empirical indication of the method being in use, for instance in clinical trials or from evaluation reports. Indirect indication means that the earliest data source used for deciding the year of introduction is a registration year or guidelines stating that it would be possible or recommended to use the method. This analysis shows that the subset of more reliable periods shows a significantly higher

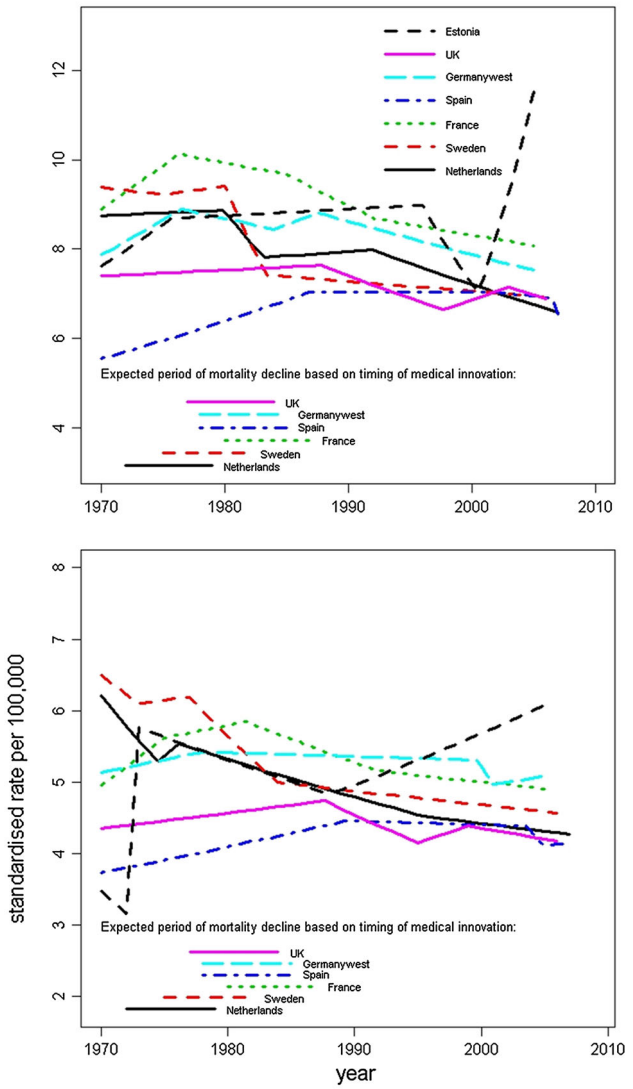

Fig. 5 Estimated standardised all-age mortality trend from leukaemia (1970–2005) for men (*upper panel*) and women (*lower panel*) and expected period of mortality decline based on introduction of improved treatment

association between innovations and mortality trends (results not shown).

Our main criterion for identifying evidence of an effect of health care is the count of countries showing an association between health care and mortality (Table 3, lower part). We counted the number of countries where we found (1) a match for both sexes, (2) a match for only one sex, and (3) no match. To explore the age-sensitivity of our results, according to the common assumption that the amenability of mortality is higher below a certain age limit, we repeated the analysis for the age range 0–74. Overall, this did not result in a closer correlation between innovation dates and changes in mortality. Only improved treatment of leukaemia shows an association after changing the age range (age specific results shown in project report).

Discussion

This study sought to determine whether the introduction of selected health care innovations coincided with a favourable change in the trend of mortality in five cancers across seven European countries. For none of the five cancers sufficient evidence for such association could be found at the national level. In addition to these new findings on a potential effect of health care innovations on population health, our study demonstrates a rigorous approach linking changes in population health to the timing of innovations. Some limitations must be mentioned: first, we focus on the timing of introduction of innovations. Yet, improvements in population health due to health care reflect three factors: the introduction of the innovation itself, further improvements in the quality with which care is delivered, and expanded coverage of the patient population. Although desirable, it is not possible, in international comparisons over time, to take account of the other factors given the absence of adequate data. Moreover, all three dimensions may progress gradually without perceptible short term changes. Second, although we based our analysis of the timing of innovations on the best available information, this information has still some uncertainty as shown by our sensitivity analysis. Innovation is a process and as such difficult to measure. For screening programmes, the timing of introduction also seems to vary between different regions and health administrative areas in the countries which limits the conclusion to be drawn on the population effectiveness of the programmes from analyses on the national level. This may for instance be the case for mammography in the United Kingdom (UK Trial of Early Detection of Breast Cancer Group 1988; Forrest 1986) and Sweden (National Board of Health and Welfare 1986). We want to mention that it was not our aim to verify whether the innovation as such was effective or not (this can be done better by clinical studies) but rather to see if mortality variations at the national level may indicate variations in the performance of medical care for certain conditions. By looking at more specific subgroups, for example in terms of region, age range or subtype of the condition, we theoretically could have increased the probability of a match, but our aim was to check whether this association exists on the national and the population level. Third, the study period was limited to 1970–2005. When the introduction was partly just before or after this period, the analysis on the national level may not be able to verify a potential linkage with a shift in mortality trend.

Table 3 Test for the likelihood of the number of matches found and counts of countries with a match between 1970 and 2005 in Estonia, France, W-Germany, Netherlands, Spain, Sweden, and UK

Likelihood test for each cause of death	Breast cancer	Cervical cancer	Testicular cancer	Hodgkin's disease	Leukaemia
Number of favourable knots, M + F for all countries	28	6	10	17	22
Expected probability of a match	0.204	0.204	0.204	0.204	0.204
Expected number of matches	5.7	1.2	2.0	3.5	4.5
Observed number of matches	5	2	2	3	5
Observed probability of a match	0.179	0.333	0.200	0.176	0.227
p value for the difference between expected and observed probability (one-sided Chi-square test)	0.364	0.254	0.488	0.384	0.396

Counts of matches for each intervention	Mammography	Tamoxifen	Introduction cervical screening	Cisplatin	High dose therapy and peripheral blood stem cell transplantation	Improved treatment (management of the disease process and its complications for younger patients)
Two sexes match	NA	NA	NA	NA	0	2
One sex matches	2	3	2	2	3	1
No match	5	4	3	5	3	3
No data	0	0	2	0	1	1
Association	no	no	no	no	no	no

For some conditions data on mortality could not be used or data on innovations were unavailable, therefore the total number of countries that could be taken into account is sometimes <7

NA not available

Fourth, there are underlying trends that have to be taken into account when interpreting the mortality trends presented here. Most importantly we cannot differentiate between incidence, prevalence and mortality. For example, incidence of testicular cancer has increased in most countries over the last 50 years. Fifth, due to our ecological study design it is not possible to interpret the observed associations on the aggregated level as a causal impact or to determine the respective role of progress in care and other factors such as smoking or alcohol consumption. Sixth, to use the mortality data across several decades and European countries implies data quality and comparability issues. However, we are confident that we did what is possible to take them into account, for example by developing an advanced method to detect biases due to ICD coding changes or by consulting national experts to understand coding habits. In rare cases where problems could not be corrected, we decided to exclude certain causes of death.

Our study relates to two strands of epidemiologic literature; the first explores the general impact of health care on cancer, the second tries to more specifically look at certain conditions as indicators of amenable mortality based on the obvious requirement that to be a useful indicator for the quality of health care, mortality from a chosen cause of death needs to be responsive to major innovations in health care. With regard to the first, the literature on this topic that we presented above found a significant effect of health care on cancer mortality. Our international comparative approach offers the opportunity to assess the effect of health care on a larger geographical scale. On the other hand it also requires the availability and reliability of national data describing the timing of innovations in health care, including the timing of their widespread adoption. Our test of likelihood combining all expected periods of mortality decline for all countries for one cause of death showed that the overall correlation between our predictions and changes in mortality is weak. Our second approach, counting the number of countries in which an association between innovations and mortality could be found, confirms this. It seems to be very difficult to prove effectiveness of specific health care innovations against cancer on the population level given available data. This is due to the incremental and simultaneous improvements in health care, the underlying trends in risk factor exposure, and the differences in the effect of health care between subtypes of cancer and age groups that are even finer than we could study here. The innovations we studied did not have a large enough effect, within the time-window that we imposed, to be visible in population mortality trends. That does not necessarily imply that the effects were small, only that the effects were smaller than those of some other determinants of cause-specific mortality trends, or were spread out over a longer period than we assumed.

The more specific issue of validating amenable mortality as an outcome of health care has been addressed in literature by two means; first, by time series analyses showing

considerable declines in amenable mortality in recent decades (Mackenbach et al. 1988, 1990; Poikolainen and Eskola 1986). This has been used to support the argument that at least part of the overall mortality decline is due to improvements in health care, but a clear correlation between therapeutic innovation and mortality on the population level has never been established. Second, several studies of geographical variation also find mortality differences among countries or regions (e.g. Charlton and Velez 1986) which are interpreted as being partly due to differences in health care, but no clear association between predictors in health care and mortality could be found. The fact that our study confirms none of the five potential indicators of amenable mortality among cancers (one of them only in the age group 0–74), led us to the conclusion that such indicators have to be interpreted with caution when being used as indicators of health care performance in a specific country (Mackenbach et al. 2013). Rates are likely to reflect the influence of health care, but also of many other factors such as life style, incidence and prevalence. Single interventions may have little measurable impact on their own because any effect is likely to be incremental as reductions in mortality typically reflect the progressive combination of multiple innovations. Our results identify the need for further analysis that takes into account not only innovations in health care but also quality of health care and population coverage which should also take into account socioeconomic differences. Such analyses crucially depend on better available data on the timing of innovations and routinely collected data linking health care use and mortality. Currently, the lack of such data is a barrier for monitoring the contribution of health care to population health, even though it undeniably exists.

Acknowledgments We thank Walter Holland for his input and valuable advices throughout the project, Esther de Vries for important comments on an earlier version of this paper and Janina Knuth for her help with layout and editing.

Conflict of interest None declared.

References

Autier P, Boniol M, Gavin A, Vatten LJ (2011) Breast cancer mortality in neighbouring European countries with different levels of screening but similar access to treatment: trend analysis of WHO mortality database. Br Med J 343. doi:10.1136/bmj.d4411

Carr-Hill RA, Hardman GF, Russell IT (1987) Variations in avoidable mortality and variations in health care resources. Lancet 1:789–792

Charlton JR, Velez R (1986) Some international comparisons of mortality amenable to medical intervention. Br Med J (Clin Res Ed) 292:295–301

Dama E, Pastore G, Mosso ML, Maule MM, Zuccolo L, Magnani C, Merletti F (2006) Time trends and prognostic factors for survival from childhood cancer: a report from the Childhood Cancer Registry of Piedmont (Italy). Eur J Pediatr 165:240–249. doi:10.1007/s00431-005-0034-7

de Kok IM, van der Aa MA, van Ballegooijen M, Siesling S, Karim-Kos HE, van Kemenade FJ, Coebergh JW, Netherlands Cancer Registry (2011) Trends in cervical cancer in the Netherlands until 2007: has the bottom been reached? Int J Cancer 128:2174–2181. doi:10.1002/ijc.25553

Department of Health and Social Security (1988) Health services management cervical cancer screening [Health Circular HC(88)1]. Department of Health and Social Security, Heywood

Duffy SW, Tabar L, Olsen AH, Vitak B, Allgood PC, Chen THH, Yen AMF, Smith RA (2010) Absolute numbers of lives saved and overdiagnosis in breast cancer screening, from a randomized trial and from the Breast Screening Programme in England. J Med Screen 17:25–30. doi:10.1258/jms.2009.009094

Ferlay J, Shin H, Bray F, Forman D, Mathers C, Parkin D (2010) GLOBOCAN 2008 v2.0, Cancer incidence and mortality worldwide: IARC Cancer Base No. 10. International Agency for Research on Cancer, France

Forrest P (1986) Breast Cancer Screening. Report to the Health Ministers of England, Wales, Scotland and Northern Ireland by a working group chaired by Professor Sir Patrick Forrest. London

Frei E 3rd, Gehan EA (1971) Definition of cure for Hodgkin's disease. Cancer Res 31:1828–1833

Gotzsche PC, Jorgensen KJ, Zahl P-H, Maehlen J (2012) Why mammography screening has not lived up to expectations from the randomised trials. Cancer Causes Control 23:15–21. doi:10.1007/s10552-011-9867-8

Hoffmann R, Plug I, Khoshaba B, McKee M, Mackenbach JP, AMIEHS working group (2012) Amenable mortality revisited: the AMIEHS study. Gac Sanit 27:199–206. doi:10.1016/j.gaceta.2012.08.004

Janssen-Heijnen MLG, Louwman WJ, Van de Poll-Franse LV, Coebergh JWW (2005) Van meten naar weten: 50 jaar kanker-registratie. Compr Cancer Cent South, Eindhoven

La Vecchia C, Bosetti C, Lucchini F, Bertuccio P, Negri E, Boyle P, Levi F (2010) Cancer mortality in Europe, 2000–2004, and an overview of trends since 1975. Ann Oncol 21:1323–1360. doi:10.1093/annonc/mdp530

Laara E, Day NE, Hakama M (1987) Trends in mortality from cervical cancer in the nordic countries: association with organised screening programes. Lancet 1:1247–1249

Leon DA (2011) Trends in European life expectancy: a salutary view. Int J Epidemiol 40:271–277. doi:10.1093/ije/dyr061

Levi F, Lucchini F, Negri E, Boyle P, Vecchia CL (2002) Trends in mortality from Hodgkin's disease in western and eastern Europe. Br J Cancer 87:291–293

Mackenbach JP, Looman CW, Kunst AE, Habbema JD, van der Maas PJ (1988) Post-1950 mortality trends and medical care: gains in life expectancy due to declines in mortality from conditions amenable to medical intervention in The Netherlands. Soc Sci Med 27:889–894

Mackenbach JP, Bouvier-Colle MH, Jougla E (1990) "Avoidable" mortality and health services: a review of aggregate data studies. J Epidemiol Community Health 44:106–111

Mackenbach JP, Hoffmann R, Khoshaba B, Plug I, Rey G, Westerling R, Pärna K, Jougla E, Alfonso J, Looman CWN, McKee M (2013) Using 'amenable mortality' as indicator of health care effectiveness in international comparisons: results of a validation study. J Epidemiol Community Health 67:139–146

Mandelblatt J, Schechter CB, Lawrence W, Yi B, Cullen J (2006) The SPECTRUM population model of the impact of screening and treatment on US breast cancer trends from 1975 to 2000: principles and practice of the model methods. J Natl Cancer Institute 36:47–55

Marmot MG, Altman DG, Cameron DA, Dewar JA, Thompson SG, Wilcox M, Independent UKPBCS (2012) The benefits and harms of breast cancer screening: an independent review. Lancet 380:1778–1786. doi:10.1016/s0140-6736(12)61611-0

McGuire WL (1978) Hormone receptors—their role in predicting prognosis and response to endocrine therapy. Semin Oncol 5:428–433

McKee M, Karanikolos M, Belcher P, Stuckler D (2012) Austerity: a failed experiment on the people of Europe. Clin Med 12:346–350

Meerding WJ, Polder JJ, de Hollander AEM, Mackenbach JP (2007) Hoe gezond zijn de zorguitgaven?. Rijksinstituut voor Volksgezondheid en Milieu, Bilthoven

National Board of Health and Welfare (1986) Screening with Mammography. SOSFS (3)

Nur U, Rachet B, Mitry E, Cooper N, Coleman MP (2008) Survival from testicular cancer in England and Wales up to 2001. Br J Cancer 99:S80–S82. doi:10.1038/sj.bjc.6604597

Office of Population Censuses and Surveys (1975/1982) Mortality statistics, Series DH2, vol 1, 9. Office of Population Censuses and Surveys, London, pp 1–14

Otto SJ, Fracheboud J, Looman CWN, Broeders MJM, Boer R, Hendriks J, Verbeek ALM, de Koning HJ (2003) Initiation of population-based mammography screening in Dutch municipalities and effect on breast-cancer mortality: a systematic review. Lancet 361:1411–1417. doi:10.1016/s0140-6736(03)13132-7

Pederson T, Mukherjee S (2011) The Emperor of All Maladies: a biography of cancer. Science 332:423. doi:10.1126/science.1206460

Plug I, Hoffmann R, Mackenbach JP (2011) AMIEHS. Avoidable mortality in the European Union: towards better indicators for the effectiveness of health systems. Final report. Department of Public Health, Erasmus Medical Center Rotterdam. http://amiehs.lshtm.ac.uk

Poikolainen K, Eskola J (1986) The effect of health services on mortality: decline in death rates from amenable and non-amenable causes in Finland, 1969–1981. Lancet 1:199–202

Rey G, Aouba A, Pavillon G, Hoffman R, Plug I, Westerling R, Jougla E, Mackenbach J (2011) Cause-specific mortality time series analysis: a general method to detect and correct for abrupt data production changes. Popul Health Metr 9:52

Robinson SP, Addada J, Green N, Wong WL, Shaw P, Chakraverty R, Goldstone AH, Macmillan A, Linch DC (2001) Response to short course ESHAP chemotherapy in relapsed and refractory lymphoma. Blood 96:246

Rogers EM (2002) Diffusion of preventive innovations. Addict Behav 27:989–993. doi:10.1016/s0306-4603(02)00300-3

Ryan R, Gross N (1943) The diffusion of hybrid seed corn in two Iowa communities. Rural Sociol 8:15–24

Tewari KS, Monk BJ (2009) Recent achievements and future developments in advanced and recurrent cervical cancer: trials of the Gynecologic Oncology Group. Semin Oncol 36:170–180. doi:10.1053/j.seminoncol.2008.12.008

UK Trial of Early Detection of Breast Cancer Group (1988) First results on mortality reduction in the UK Trial of Early detection of breast cancer. Lancet 8608(2):411–416

Westerling R (1996) Studies of avoidable factors influencing death: a call for explicit criteria. Q Health Care 5:159–165

Zhang B, Su Z, Qiu P (2009) On jump detection in regression curves using local polynomial Kernel estimation. Pak J Stat 25:505–528