

## Review Paper

# Progress of anticancer drugs in reducing mortality from selected cancers in Europe: an assessment

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**Trends in mortality from four groups of cancers amenable to anti-cancer treatments (testicular cancer, Hodgkin's disease, leukemias and childhood cancers) between the late 1950s and the late 1980s were analyzed for the 23 larger European countries. In Western Europe, newer treatments led to the avoidance of approximately 1000 deaths from testicular cancer, 4000 from Hodgkin's disease, 4000 from leukemias, and 2500 from childhood cancers. In Eastern Europe, declines in mortality were observed only for childhood cancers, for a total of about 500 fewer deaths per year. Thus, approximately 11 000 deaths per year were avoided in Europe by newer cancer treatments, corresponding to 1% cancer deaths registered in the 23 larger European countries. A few thousand further deaths from these cancers could be avoided through more widespread and rational utilization of currently available therapies, particularly in Eastern Europe.**

**Key words:** Cancer, childhood neoplasms, Hodgkin's disease, leukemias, mortality, testicular cancer.

## Introduction

Over the last decade, the issue of cancer curability by chemotherapy has been subject to widespread, and often controversial debate. In the early 1980s, estimates of cancer patients cured by chemotherapy in the United States ranged between 40 000<sup>1</sup> and 5000,<sup>2</sup> and widely different estimates were often provided not only by different, but also by the same authors.<sup>1,3,4</sup>

Most of these apparent discrepancies are essentially due to the interpretation of data. Trends in cancer mortality have been analysed for several decades and there is general consensus that, with the notable exception of the tobacco-related cancer epidemic and of the substantial declines in stomach and cervical cancer mortality, only limited systematic changes have been observed for any of the major cancer sites over the last few decades in middle-aged populations.<sup>5,6</sup> Some controversy has arisen, since a few specific cancer sites, such as brain, prostate or myeloma, have apparently increased in the elderly. These sites, however, are among the most widely affected by improved diagnostic procedures and certification, and it is therefore possible that most of the apparent rises are artefactual, as confirmed by inspection of trends in selected areas with high standards of cancer registration.<sup>7–11</sup>

For common cancer sites, it is more difficult to understand and quantify the potential impact of improved treatment and survival. For several of these neoplasms, there is little basis to suggest any material improvement, but even in the case of breast cancer, where a 10% improved survival is possible,<sup>12</sup> this can easily be missed within the changes in incidence. Mortality, in fact, reflects both variations in survival and incidence rates, but the latter are unfortunately not available and reliable enough for large areas and meaningful periods of time.

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There are, however, a few selected neoplasms or groups of neoplasms for which the progress in therapy over the last few decades has been substantial, and for which the corresponding public health impact on national mortality rates is both evaluable and quantifiable on the basis of death certification data. These are essentially lymphoreticular neoplasms and germ cell tumors. Also for these cancers, however, the availability and utilization of efficacious therapies has not been the same in various countries and areas, and the consequent impact in terms of avoided deaths has not been completely exploited in all areas.

This article will summarize changes in mortality from selected cancer sites (testis, Hodgkin's disease, leukemias and all childhood cancers) in various European countries between the mid-1950s and the late 1980s, and evaluate the corresponding impact in terms of public health and avoided deaths.

## Testis

Table 1 gives the overall age-standardized mortality rates from testicular cancer in 16 Western and 7 Eastern European countries in the late 1950s and in the mid to late 1980s.

In all Western European countries, except Spain, mortality rates from testicular cancer were lower in the mid-1980s as compared to three decades earlier. The average fall in rates was nearly 30% in the whole of Western Europe, corresponding to the avoidance of approximately 500 deaths per year if the rates of the late 1950s were applied to the population structure of the mid-1980s.

The progress may well have been larger, since incidence rates of testicular cancer have been rising in most developed areas over the last decades. In Eastern Europe, indeed, where the impact of newer therapies has probably been

**Table 1.** Overall death certification rates<sup>a</sup>/100 000 people (and numbers of deaths) from testicular cancer in selected European countries, 1955–59 and 1985–88

Country (year)	Males			Females		
	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates
<b>Western Europe</b>						
Austria	0.69(24)	0.62(27)	–10	1.66(79)	0.68(48)	–59
Belgium	0.46(24)	0.18(7)	–61	1.28(70)	0.85(32)	–34
Denmark	1.87(43)	0.91(28)	–51	1.52(39)	0.33(15)	–78
Finland	0.53(10)	0.29(8)	–45	0.78(19)	0.38(17)	–51
France	0.62(148)	0.51(172)	–18	1.04(273)	0.36(152)	–65
W. Germany	0.86(227)	0.68(256)	–21	1.19(387)	0.57(321)	–52
Greece (1965–69)	0.28(27)	0.34(20)	–21	0.87(47)	0.58(42)	–33
Ireland	0.55(8)	0.41(8)	–25	1.02(15)	0.42(11)	–59
Italy	0.72(191)	0.43(152)	–40	1.45(414)	0.67(286)	–54
The Netherlands	1.25(69)	0.41(36)	–67	1.40(82)	0.47(56)	–66
Norway	1.24(23)	0.51(14)	–59	1.23(26)	0.51(18)	–59
Portugal (1980–84)	0.27(15)	0.31(18)	–15	0.45(29)	0.35(25)	–22
Spain	0.12(18)	0.23(52) <sup>b</sup>	+92	0.55(91)	0.45(121)	–18
Sweden	0.77(30)	0.33(18)	–57	1.14(55)	0.38(29)	–67
Switzerland	1.00(27)	0.78(30)	–22	1.46(45)	0.70(39)	–52
United Kingdom	0.78(213)	0.45(147)	–42	1.07(358)	0.49(213)	–54
<b>Eastern Europe</b>						
Bulgaria (1965–69)	0.80(29)	1.16(57)	+45	0.74(36)	0.53(30)	–28
Czechoslovakia	0.46(31)	1.12(95)	+143	1.49(116)	0.84(98)	–44
E. Germany (1975–79)	1.58(139)	1.65(156)	+4	0.72(93)	0.81(110)	+13
Hungary (1970–74)	1.01(57)	1.21(71)	+20	0.58(41)	0.75(64)	+29
Poland (1960–64)	0.30(54)	0.75(154)	+150	0.66(144)	0.69(166)	+5
Rumania (1965–69)	0.42(44)	0.50(59) <sup>b</sup>	+19	0.53(63)	0.57(73) <sup>b</sup>	+8
Yugoslavia (1960–64)	0.35(32)	0.52(64)	+49	0.64(64)	0.84(121)	+31

<sup>a</sup> Age-standardized rates on the world standard population.

<sup>b</sup> 1980–84.

limited, mortality rates increased by an average of approximately 60%. Thus the absolute advantage of newer therapies on testicular cancer mortality in Western Europe may well be substantially larger, and possibly approach 1000 deaths avoided per year. Consequently, the absence or delay in availability or application of newer therapeutic approaches for testicular cancer in countries of Eastern Europe has probably resulted in an excess of 200 to 400 deaths per year. The importance of these figures is further stressed by the age distribution of testicular cancer, which shows an early peak (including seminomas and teratomas, i.e. the histotypes largely affected by improved therapy) in the third decade of life.<sup>9</sup>

Response rates in up to one-third of the patients treated were observed in the 1960s and 1970s using combination of drugs including actinomycin D, chlorambucil and methotrexate, but a major advancement was registered after the

addition of cisplatin to chemotherapy in the mid-1970s. This led to cure rates in the order of 80%, which were subsequently further improved by refinements of the schemes.<sup>13</sup> These values underline the importance of achieving adequate treatment standards in various areas of the world.

### Hodgkin's disease

Table 2 gives age-standardized mortality rates and numbers of certified deaths from Hodgkin's disease in 16 Western and 7 Eastern European countries in the late 1950s (again, before definition and introduction of effective therapy), and in the most recent calendar period (usually, mid to late 1980s). In all Western countries, Hodgkin's disease mortality fell substantially, generally starting from the late 1960s or early 1970s. The overall mean decline was 50% in both sexes, and figures for most countries were similar to this average value. Only

**Table 2.** Overall death certification rates<sup>a</sup>/100 000 people (and numbers of deaths) from Hodgkin's disease in selected European countries, 1955–59 and 1985–88

Country (year)	Males			Females		
	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates
<b>Western Europe</b>						
Austria	2.37(93)	1.15(54)	–51	1.66(79)	0.68(48)	–59
Belgium	2.39(127)	1.18(40)	–51	1.28(70)	0.85(32)	–34
Denmark	2.35(58)	0.79(29)	–66	1.52(39)	0.33(15)	–78
Finland	1.88(39)	1.01(30)	–46	0.78(19)	0.38(17)	–51
France	1.62(337)	0.75(261)	–54	1.04(273)	0.36(152)	–65
W. Germany	2.08(572)	0.99(397)	–52	1.19(387)	0.57(321)	–52
Greece (1965–69)	1.86(87)	1.21(81)	–35	0.87(47)	0.58(42)	–33
Ireland	2.08(32)	1.37(26)	–34	1.02(15)	0.42(11)	–59
Italy	2.37(615)	1.16(420)	–51	1.45(414)	0.67(286)	–54
The Netherlands	2.08(118)	0.96(86)	–54	1.40(82)	0.47(56)	–66
Norway	1.89(37)	0.72(21)	–62	1.23(26)	0.51(18)	–59
Portugal (1980–84)	0.94(50)	0.68(40)	–28	0.45(29)	0.35(25)	–22
Spain	1.06(155)	0.82(178)	–23	0.55(91)	0.45(121)	–18
Sweden	1.97(88)	0.59(38)	–70	1.14(55)	0.38(29)	–67
Switzerland	1.90(53)	1.16(51)	–39	1.46(45)	0.70(39)	–52
United Kingdom	1.99(570)	0.85(299)	–57	1.07(358)	0.49(213)	–54
<b>Eastern Europe</b>						
Bulgaria (1965–69)	1.45(68)	1.02(57)	–30	0.74(36)	0.53(30)	–28
Czechoslovakia	2.75(192)	1.54(133)	–44	1.49(116)	0.84(98)	–44
E. Germany (1975–79)	1.39(132)	1.33(127)	–4	0.72(93)	0.81(110)	+13
Hungary (1970–74)	1.06(65)	1.25(80)	+18	0.58(41)	0.75(64)	+29
Poland (1960–64)	1.62(312)	1.56(309)	–4	0.66(144)	0.69(166)	+5
Rumania (1965–69)	1.15(116)	1.15(138) <sup>b</sup>	—	0.53(63)	0.57(73) <sup>b</sup>	+8
Yugoslavia (1960–64)	1.14(100)	1.53(193)	+34	0.64(64)	0.84(121)	+31

<sup>a</sup> Age-standardized rates on the world standard population.

<sup>b</sup> 1980–84.

some Nordic countries (Denmark and Sweden) showed larger declines, approaching 70%, and rates in these countries started to fall somewhat earlier. These countries now have mortality rates from Hodgkin's disease among the lowest in Europe. In contrast, the falls were observed later and were more limited in absolute terms in Spain and Greece, ranging between 20 and 30%.

This pattern of trends confirms that efficacious treatments for Hodgkin's disease have become available and have been adopted in all Western Europe, although their utilization has not been uniform and there is certainly still scope for further improvements in several areas, not only in terms of further developments and advancements in the treatment of the disease (since there is no evidence of flattening of the decline), but also in relation to better utilization of already developed therapies.

The declines in Hodgkin's disease mortality were observed in children (under 15 years), young adults (15 to 34 years) and in middle age as well (35 to 64 years), and, although they tended to be proportionally greater in the young, in absolute terms they were larger in middle age. Trends were less consistent over age 65, although some decline was observed in several western European countries, also in the elderly.

In absolute terms, the declines observed in Hodgkin's disease mortality in Western Europe correspond to the avoidance of over 3000 deaths per year, and this figure could well approach 4000 if the more favorable trends were obtained in all areas.

No consistent trend in Hodgkin's disease mortality was observed in the seven Eastern European countries considered. Some fall was registered in Bulgaria (approximately 30%) and Czechoslovakia (45%), but in other countries rates remained stable or increased (Hungary, Yugoslavia) over the last two decades. The average changes in rates in Eastern Europe were -5% for males and +2% for females, indicating no overall material progress. Assuming that trends comparable to those registered in Western Europe were observed in the East, this could have avoided between 800 and 1000 deaths per year.

These rates may be somewhat influenced by uncertainties in diagnosis and certification, although Hodgkin's disease has long been a well-recognized and defined pathological entity,<sup>14</sup> and problems of diagnosis and certification can explain only a minor fraction of the systematic trends observed. The latter can consequently be

largely attributed to the role of newer radio- and chemotherapy techniques in the treatment of the disease.

These advancements have developed starting from the 1950s, at least in research settings.<sup>15,16</sup> The delay in the transfer of the advancements to national mortality rates and the persisting differences in the pattern of trends in various areas have to be considered critically.

## Leukemias

Changes in mortality from leukemia between the late 1950s and the late 1980s in populations aged under 65 are presented in Table 3. Again, rates were consistently downwards in all European countries except Portugal and Spain (comparison for these countries was however possible only in the more recent calendar period). Leukemia mortality rates were up in the elderly, probably reflecting improved diagnosis and certification of the disease,<sup>17</sup> and the pattern was therefore much less consistent when overall rates were considered (data not shown).

The average decline for Western Europe was 26% for males and 33% for females, corresponding to the avoidance of approximately 4000 deaths per year. These declines were greater in childhood, but were generally evident throughout young adult and middle age. Efficacious chemotherapy for leukemia (and, particularly, acute lymphoblastic leukemia) has been available since the late 1950s,<sup>18,19</sup> and its impact on national mortality rates has been observed starting from the late 1960s or early 1970s.

As for Hodgkin's disease, the decline was larger for Nordic countries (over 40% in both sexes), and more limited in Central and particularly Southern Europe. Thus the theoretical impact of rational application of currently available therapies may well be over 5000 avoided deaths per year in Western Europe.

For leukemias under age 65, some decline in mortality was observed in most Eastern countries too, averaging, over the period considered, 8% in males and 11% in females. Most of these declines started from the late 1970s or early 1980s. This corresponds to the avoidance of approximately 400 deaths from leukemia per year, a figure which could be raised up to four-fold (to 1500 deaths per year) assuming a generalized application of the best improvements observed in some Nordic countries.

As for Hodgkin's disease, difficulties and uncertainties in diagnosis and certification hinder

**Table 3.** Overall death certification rates<sup>a</sup>/100 000 people aged 0–64 years (and numbers of deaths) from leukemia in selected European countries, 1955–59 and 1985–88

Country (year)	Males			Females		
	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates
<b>Western Europe</b>						
Austria	4.50(145)	2.99(111)	–34	3.35(123)	2.10(85)	–37
Belgium	4.35(185)	3.18(80)	–27	3.47(151)	2.30(56)	–34
Denmark	5.06(106)	3.88(99)	–23	3.89(85)	2.78(67)	–29
Finland	4.52(88)	3.32(77)	–27	3.55(75)	2.11(52)	–41
France	4.74(967)	3.44(925)	–27	3.76(794)	2.35(636)	–38
W. Germany	4.22(980)	3.06(945)	–27	3.33(887)	2.10(688)	–37
Greece (1965–69)	5.33(211)	3.25(160)	–39	3.80(153)	2.44(123)	–36
Ireland	3.67(49)	2.81(44)	–23	2.84(37)	2.11(33)	–26
Italy	4.50(983)	3.87(1109)	–14	3.52(800)	2.77(827)	–21
The Netherlands	4.73(240)	2.87(202)	–39	3.63(188)	2.20(152)	–39
Norway	4.96(83)	2.88(57)	–42	3.52(60)	2.07(41)	–41
Portugal	3.04(118)	3.32(158)	+9	2.59(110)	2.58(125)	—
Spain	2.69(354)	3.25(588)	+21	1.96(270)	2.67(494)	+36
Sweden	4.85(169)	2.65(106)	–45	3.90(136)	2.17(86)	–44
Switzerland	4.63(107)	2.92(93)	–37	3.45(84)	2.19(72)	–37
United Kingdom	3.94(937)	3.02(834)	–23	3.01(753)	2.21(612)	–27
<b>Eastern Europe</b>						
Bulgaria (1965–69)	4.05(159)	3.88(176)	–4	3.44(132)	2.86(132)	–17
Czechoslovakia	4.42(285)	3.96(296)	–10	3.07(209)	3.05(239)	–1
E. Germany (1975–79)	3.80(208)	3.40(267)	–11	2.85(191)	2.44(218)	–14
Hungary	4.26(195)	4.33(230)	+2	3.12(160)	2.88(167)	–8
Poland (1960–64)	3.80(524)	3.57(627)	–6	2.99(441)	2.50(467)	+5
Rumania (1965–69)	3.85(344)	3.52(365) <sup>b</sup>	–9	3.05(278)	2.75(292) <sup>b</sup>	–10
Yugoslavia (1960–64)	3.55(401)	2.88(322)	–19	2.76(328)	1.97(236)	–29

<sup>a</sup> Age-standardized rates on the world standard population.<sup>b</sup> 1980–84.

any more precise assessment, on a population scale, of the impact of newer therapies. The general pattern emerging from this, though simplified, overview is clear enough, however, to allow a general conclusion and quantitative assessment.

### Childhood cancer

Table 4 presents mortality rates from all childhood cancers (before age 15). All Western European countries, except Portugal and Spain, showed substantial declines in mortality over the last decades, for an average fall of over 40% in both sexes and an estimated total number of approximately 2500 avoided deaths.

Favorable trends were observed also in Eastern Europe (except Rumania), but the declines were approximately only 20%, with an estimated number of about 500 deaths avoided per year.

Over one-third of these deaths are due to

leukemia alone, and hence estimates of avoided deaths are not mutually exclusive with those previously discussed. Still, substantial improvements in survival rates have been observed in all principal types of childhood cancer (except, perhaps, Ewing's sarcoma<sup>20</sup>). These advances have largely been due to the development of effective multidrug chemotherapy protocols, together with the introduction of various supportive measures to overcome toxicity as well as the availability of megavoltage radiation and improved diagnostic techniques.<sup>20–22</sup>

Even in Western countries, better survival rates have been observed in children treated in specialist centers,<sup>20,23</sup> and the declines have been somewhat delayed in some countries such as Germany, Italy, The Netherlands, Norway, Portugal, Spain and Sweden as compared to Belgium, Denmark, France, Switzerland and the United Kingdom.

Almost certainly, therefore, there is scope and

**Table 4.** Overall death certification rates<sup>a</sup>/100 000 people aged 0–14 years (and numbers of deaths) from all neoplasms in selected European countries, 1955–59 and 1985–88

Country (year)	Males			Females		
	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates	1955–59 Rate (No of deaths per year)	1985–88 Rate (No of deaths per year)	Percent difference in rates
<b>Western Europe</b>						
Austria	10.78(81)	4.20(29)	–61	8.78(64)	3.46(22)	–61
Belgium	9.69(96)	5.97(28)	–38	7.54(74)	5.29(23)	–30
Denmark	11.45(66)	5.79(28)	–49	8.51(47)	5.23(28)	–39
Finland	9.55(62)	4.96(24)	–48	8.04(51)	2.82(13)	–65
France	10.29(580)	5.56(314)	–46	8.19(443)	4.44(237)	–46
W. Germany	9.49(522)	4.62(212)	–51	8.18(427)	3.65(160)	–55
Greece (1965–69)	11.06(123)	5.78(61)	–48	8.94(92)	4.56(44)	–49
Ireland	8.13(35)	4.67(25)	–43	6.71(28)	3.31(17)	–51
Italy	11.00(669)	6.57(365)	–40	8.62(497)	5.05(267)	–41
The Netherlands	9.76(162)	4.54(63)	–53	8.41(131)	3.95(52)	–53
Norway	11.23(51)	5.46(23)	–51	9.37(40)	4.26(16)	–55
Portugal	6.99(91)	7.62(89)	+9	5.62(70)	5.95(67)	+6
Spain	6.44(260)	6.62(299)	+3	5.24(202)	5.24(228)	—
Sweden	10.25(87)	5.16(40)	–50	9.62(76)	4.64(32)	–52
Switzerland	11.08(69)	5.03(29)	–55	8.51(51)	3.95(22)	–54
United Kingdom	9.47(561)	4.42(245)	–53	7.85(442)	4.15(215)	–47
<b>Eastern Europe</b>						
Bulgaria (1965–69)	10.46(102)	8.70(81)	–17	8.84(81)	5.93(53)	–33
Czechoslovakia	10.08(187)	7.00(132)	–31	7.40(131)	5.60(98)	–24
E. Germany (1975–79)	7.60(107)	5.34(87)	–30	5.86(78)	4.24(66)	–28
Hungary	9.57(123)	6.93(78)	–28	7.12(88)	5.81(60)	–18
Poland (1960–64)	8.52(425)	6.65(323)	–22	7.23(342)	5.57(256)	–23
Rumania (1965–69)	9.88(246)	9.56(280) <sup>b</sup>	–3	7.70(180)	7.86(218) <sup>b</sup>	+2
Yugoslavia (1960–64)	7.60(176)	5.99(171)	–21	5.94(130)	4.81(126)	–19

<sup>a</sup> Age-standardized rates on the world standard population.<sup>b</sup> 1980–84.

possibility for some further improvement through even better adoption of currently available techniques. These possibilities are even larger in Eastern Europe, where at least 500 further deaths from childhood cancer per year might be avoided through widespread adoption of efficacious treatments.

## Summary and conclusions

An analysis of trends in mortality from four types of cancer whose prognosis has clearly improved following the adoption of newer therapies, indicates that approximately 11 000 deaths per year from testicular cancer, Hodgkin's disease, leukemias and childhood cancer have been avoided in Western Europe, and a few hundred from leukemia and childhood cancers in Eastern Europe, as well. Furthermore, it also suggests that a few thousand deaths from these cancers could be avoided in Europe, simply through

more widespread availability and rational utilization of currently available therapies, leading to a theoretical potential impact of over 15 000 deaths avoided per year.

This figure represents about 1.4% of the 1 120 000 cancer deaths registered per year in the 23 larger European countries considered. The public health and social impact is however much larger than the crude percentage, since most of these avoided deaths are in the young and middle-aged population, and are consequently much more relevant in terms of years of life saved.

A simple approach applied to other cancer sites did not allow estimation of any potential impact of therapies. Mortality from cancer of the stomach and of the cervix uteri declined substantially in European countries, but these favorable trends cannot be attributed to therapy (since modern surgery for these neoplasms was already available in the 1950s), nor to better control or identified risk factors, although at least part of the

fall in cervical cancer mortality is due to screening.<sup>24</sup> It is nonetheless possible that some progress is concealed in the trends in mortality from a few common cancers, particularly breast,<sup>12</sup> and, even if limited in terms of percentage decrease of mortality, this would have a major public health impact on account of the much higher incidence of breast cancer.

For several reasons, therefore, the estimates given should be taken as a lower limit of the impact of the progress induced by anti-cancer drugs in Europe. This cannot eclipse, however, the second major message emerging from this report, that there is an appreciable scope for further improvement in cancer treatment in Europe through a more widespread and rational application of currently available treatments.

However large the additional gains due to rationalization of available therapeutic instruments may be, they would in any case be minor compared to the scope of prevention that could be achieved through the application of available knowledge on cancer causes. Between 250 000 and 300 000 cancer deaths per year could be avoided in the 23 countries considered through elimination of tobacco smoking, and between 40 000 and 60 000 through a reduction in alcohol consumption. Thus, a meaningful degree of cancer control by the year 2000 (such as the 15% reduction proposed by the 'Europe Against Cancer' program of the Commission of the European Communities<sup>25</sup>) can only be achieved by a more widespread adoption of basic measures of prevention.<sup>26</sup>

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