Original article

Changes in life expectancy for cancer patients over time since diagnosis

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HIGHLIGHTS

- Research question: how cancer impacts on LE changes during patients' entire life
- LE increased in patients surviving the first years and decreasing thereafter.
- Patients' LE in the end approached but seldom reached the general population's LE.
- This method describes when cancer survivors' excess risk of death became negligible.

GRAPHICAL ABSTRACT

- Life expectancy indicator is easy to be understood and interpreted by patients.
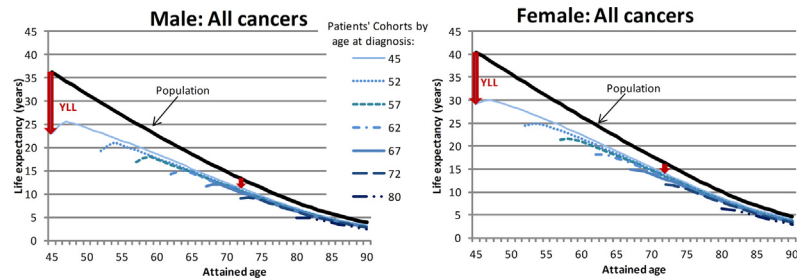
YLL= Years of life lost, difference between patients' LE and that of the age and sex matched general population

ABSTRACT

The aims of this study were to provide life expectancy (LE) estimates of cancer patients at diagnosis and LE changes over time since diagnosis to describe the impact of cancer during patients' entire lives. Cancer patients' LE was calculated by standard period life table methodology using the relative survival of Italian patients diagnosed in population-based cancer registries in 1985–2011 with follow-up to 2013. Data were smoothed using a polynomial model and years of life lost (YLL) were calculated as the difference between patients' LE and that of the age- and sex-matched general population. The YLL at diagnosis was highest at the youngest age at diagnosis, steadily decreasing thereafter. For patients diagnosed at age 45 years, the YLL was above 20 for lung and ovarian cancers and below 6 for thyroid cancer in women and melanoma in men. LE progressively increased in patients surviving the first years, decreasing thereafter, to approach that of the general population. YLL in the long run mainly depends on attained age. Providing quantitative data is essential to better define clinical follow-up and plan health care resource allocation. These results help assess when the excess risk of death from tumour becomes negligible in cancer survivors.

Introduction

Life expectancy (LE), the average number of years a homogeneous group of individuals is expected to live at a certain age, is a widely used indicator in demographical analysis [1,2]. It depends on the complete mortality profile observed in the considered population group, but not on the age structure of the population; it is therefore useful as a standardised indicator when comparing overall mortality patterns among different populations. The comparison of patients' LE with respect to their cancer-free peers is a straightforward indicator of the disease burden; it provides "real-world" estimations for the actual impact of cancer on the population of interest and conveys what a cancer diagnosis entails in terms of future life perspectives. Differences in LE with respect to cancer-free peers are also more intuitive concepts with respect to relative survival to express at the personal level the life-threatening implications of the disease [3,4].

Most estimates of cancer patients' LE only refer to the time of diagnosis as an estimate of the disease burden [3–9]. However, its relevance is not limited to the time of diagnosis but becomes even stronger for long-term survivors. Nonetheless, to the best of our knowledge, only one study has provided cancer survivors' LE estimates not only by sex and age at diagnosis, but also by time since diagnosis and consequently by attained age after diagnosis [10]. This detail is important because it allows to follow the patient over time and update his/her LE conditioned to have survived up to that time and specific age. LE at a given age, for example at 70 years and after 10 years since diagnosis compared with that of healthy people of the same age and sex, is more sensible [10] information for patients than a probabilistic concept as conditional survival, often in the long term very close to 100%.

Several aspects of survivorship are modified by time since cancer diagnosis and LE of patients, in particular quality of life [11].

Current and future approaches to communication of LEs to patients should be based on solid evidence [3,4], presently scant.

The aim of this paper was to provide, for the first time in Italy, LE estimates for major cancer types by sex, age at diagnosis, and attained age after diagnosis, and to compare them with those from the age- and sex-matched general Italian population in order to better describe the changing impact of cancer on LE over time.

Material and methods

This study used data collected by the network of population-based Italian cancer registries [8], which agreed to participate in the study and with at least 18 years of cancer registration as of December 31, 2011 (that is, Ferrara, Genova, Modena, Parma, Ragusa, Sassari, Varese, and Veneto, representing 10% of the entire Italian population in 2010) [8,12].

This study included all malignant tumours (International Classification of Diseases, Tenth Revision ICD-10 C00-C43, C45-C96) and those with benign/uncertain behaviour or *in situ* bladder cancers. Non-melanoma skin cancers (ICD-10 C44) and cases identified only by their death certificates or autopsy findings were excluded. Only first diagnoses of cancers were retained. The third International Classification of Diseases for Oncology (ICD-O-3) was used to identify morphology subtypes.

Data from 722,737 Italian cancer patients were extracted in January 2017 from the AIRTUM database. Those included were diagnosed during the period 1985–2011 and followed-up for vital status until December 31, 2013.

In order to obtain stable estimates, all cancers-age-sex combinations that had no relative survival (RS) estimates or annual RS estimates up to 13 years of follow-up based on less than five cases were not considered in the analysis. Therefore, the selected cancers were stomach, colon, rectum, anus, lung, melanoma, bladder,

thyroid, non-Hodgkin lymphoma, and leukaemias for both sexes; breast, cervix, corpus uteri, and ovary for females; and larynx, prostate, and testis for males (Supplementary material Table 1). LE of the general population was provided by the National Institute of Statistics (ISTAT) based on age-specific survival probabilities observed in all birth cohorts born at any time and living during a single calendar period, 2010. LE of the general population was calculated using the standard period life table method [1]. A period life table describes what would happen to a hypothetical cohort of persons if they experienced the age-specific mortality risks observed during the reference period. This assumption provides a useful representation of current mortality risks.

LE of the general population in the period 2009–2011 was compared with those of patients born at any time and diagnosed in 1985–2011. Cancer patients' LE was calculated in four steps. In step one, RS of cancer patients was estimated by the period method [13] for coherence with the population life table. RS estimates using the period approach were estimated for the period 2009–2011 using the survival experience of patients diagnosed in 1985–2011. The period estimate combined the survival of 25 different three-year cohorts of diagnosis. One-year RS was estimated from patients diagnosed in 2009–2011, 2-year RS from patients diagnosed in 2008–2010 and surviving at least one year, and so on up to the specific 25-year RS estimated from patients diagnosed in 1985–1987 and surviving at least 24 years after diagnosis. Interval-specific RSs were estimated using the Ederer-2 approach [14] for each sex, cancer type, and by seven age classes, in years (40–49, 50–54, 55–59, 60–64, 65–69, 70–74, and 75–84 years). The first (40–49 years) and last (75–84 years) age classes were wider, the former because of the lower number of cases and the latter because of the requirement for sufficient numbers of long-term survivors to properly estimate LE. In addition, for thyroid cancer and Hodgkin lymphoma, the analyses started from the age of 15 years (by 5-year age classes). Finally, for testis cancer, the first age class included patients aged 15–24 years. The number of cases of the selected cancers according to age class entering into each survival period life table at the first interval after diagnosis is reported in the Supplementary material (Supplementary material Table 1). The interval-specific RS of cancer patients was then derived from the age at diagnosis and the time since diagnosis. In step two, cancer-specific annual death hazard up to age 119 years, not observable using the current 23-year-long dataset, was estimated for each age class using the moving average method. Ten-year moving average was used to reach age 119 years for each cohort of diagnosis. Step three consisted of adding patients' excess mortality risk due to cancer to the general population's mortality risk to obtain their overall risk for all causes, and cancer patients' LE was calculated with the same method used for the general population [1]. In this calculation, cohorts of patients were considered as centred at the mid-point of the age class at diagnosis (ages 17, 22, ..., 45, 52, ..., 80 years). Standard errors of cancer patients' LE estimates were calculated using the delta method. Details of these first three steps are described by Capocaccia et al. [10]. The final step consisted of applying a smoothing algorithm to stabilise the cancer patients' LE values obtained after the previous steps. To this end, a third degree polynomial model was fitted to these LE values (up to a maximum age of 90 years) for each sex and cancer, with age and time since diagnosis as the independent variables and the log of the differences between the general population (pop) and cancer patients' (cp) LE as the dependent variable:

$$\text{Log}(\text{LE}_{pop} - \text{LE}_{cp}) = \alpha_1 * \text{age} + \alpha_2 * \text{age}^2 + \alpha_3 * \text{age}^3 + \beta_1 * t + \beta_2 * t^2 + \beta_3 * t^3 + \gamma_1 * t_1 + \gamma_2 * t_2 + \gamma_3 * t_3,$$

where age is the age at diagnosis, t is the time since diagnosis, and t_1, t_2, and t_3 are indicator variables for the first three years following

diagnosis, in which mortality risk is often very high and rapidly changing. The purpose of this model is to assure continuity of the LE function with time after diagnosis and its consistency across age classes. The model provides a very good fit of the data with a determination coefficient always >0.8 and in most cases >0.9.

The LE by age and time since diagnosis for the two sexes combined was obtained by weighting the sex-specific estimates with the corresponding number of cases alive at the considered time. Finally, years of life lost (YLL) was calculated as the difference between LE_{pop} and LE_{cp} estimated using the polynomial model, which represents the LE gap of survivors of the considered cancers with respect to sex- and age-matched cancer-free population. All analyses were conducted using Stata Statistical Software: Release 13 (StataCorp, College Station, TX, USA).

Results

Figs. 1 and 2 show all cancers combined and three common cancer sites, the LE patterns by attained age of the female and male patients, according to the age at diagnosis, compared with the general population.

The complete set of figures including the LE estimates, by cancer, sex, age at diagnosis, and attained age are available online (Supplementary material Figs. A and B).

Table 1 reports the LE and YLL for all cancer types combined for females, males, and both sexes by age at diagnosis and at specific time points after diagnosis (0, 1, 5, 10, and 15 years).

In the Supplementary material, the number of cases (Supplementary material Table 1) and long-term (10-year) period RS estimates (Supplementary material Table 2) are also reported for the considered cancer sites, sex, and age at diagnosis, as the RSs are the major drivers of LE indicators. Furthermore, Supplementary material Tables 3 and 4 report the LE and YLL of female and male cancer patients by age at diagnosis for all considered cancers at specific time points (0, 1, 5, 10, and 15 years) after diagnosis.

Sex

The estimated LE of women diagnosed with any cancer (Fig. 1 and Table 1) presented some general characteristics common to most of the considered site-specific cancers. The largest drop in LE, with respect to cancer-free women of the same age, occurred immediately at diagnosis (Fig. 1). The drop in LE was highest for the youngest age classes (YLL = 11.2 years for those diagnosed at age 45 years) and progressively decreased with age at diagnosis, from 9.3 YLL at age 52 years up to 3.7 YLL at age 80 years (Table 1). After such a considerable initial drop, the patients' LE tended to increase in the first few years after diagnosis for those surviving the high death risk concentrated in these years. The initial increase was progressively less pronounced with increasing age at diagnosis and disappeared in women diagnosed after age 62 years. In the third phase, the patients' LE started to decrease again, approaching but never reaching that of the general population. In the third phase, the cancer patients' loss of LE with respect to the general population was highly dependent on the attained age and only to a lesser extent on the time since diagnosis. For example, the estimated YLL of women aged 72 years diagnosed 15 years earlier (that is, at age 57 years) was 2.8, while the YLL of women the same age but diagnosed only five years earlier (that is, at age 67 years) was 3.4 (Fig. 1 and Table 1).

The general picture was similar for men diagnosed with any cancer (Fig. 2 and Table 1), with some differences, partly due to the different cancer site distribution. The LE of men, both cancer-free and cancer patients, was lower with respect to women, as well-known from demographic data. The estimated increase in LE

Fig. 1. Life expectancy of the general population (black) and of each age class at diagnosis by age for all cancers; colon, rectum, and anus; lung; and breast, Italy, females.
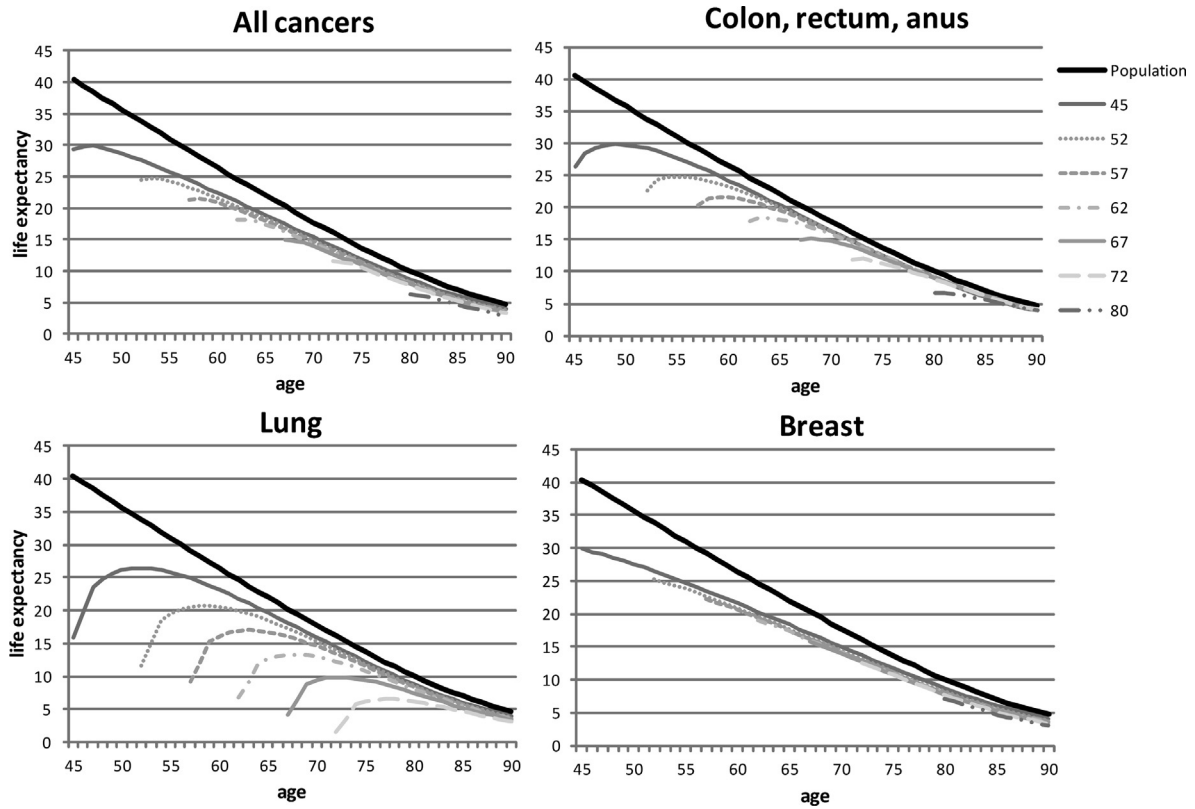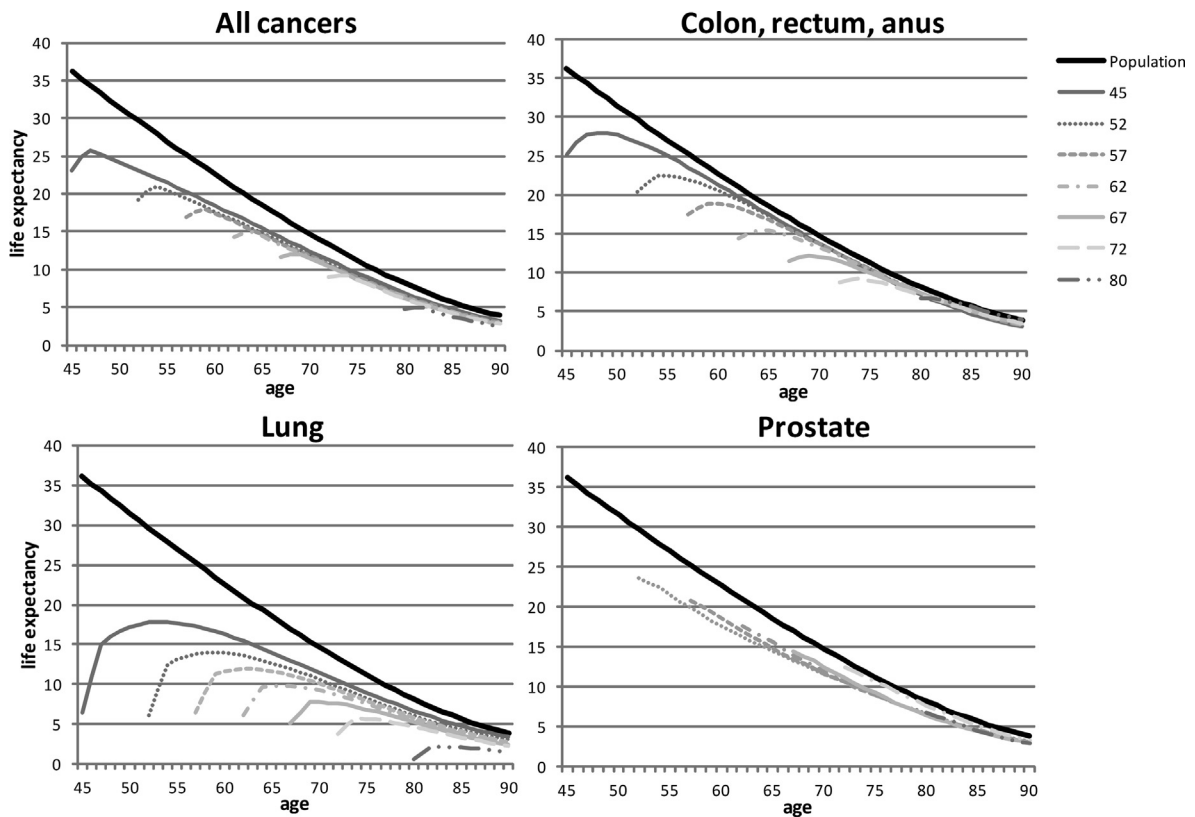

Fig. 2. Life expectancy of the general population (black) and of each age class at diagnosis by age for all cancers; colon, rectum, and anus; lung; and prostate, Italy, males.

Table 1

Life expectancy (LE) and years of life lost (YLL) of all cancer patients with respect to the age-matched cancer-free population at specific time points after diagnosis (0, 1, 5, 10, and 15 years) by sex and age at diagnosis.

Sex	Years since diagnosis	LE (YLL)						
		Age at diagnosis						
		45	52	57	62	67	72	80
Females	0	29.3 (11.2)	24.5 (9.3)	21.4 (7.7)	18.2 (6.4)	14.9 (5.3)	11.7 (4.4)	6.3 (3.7)
	1	29.7 (9.8)	24.7 (8.2)	21.5 (6.8)	18.1 (5.7)	14.8 (4.6)	11.4 (3.9)	6.2 (3.2)
	5	28.6 (7.0)	23.3 (5.8)	19.8 (4.9)	16.2 (4.0)	12.7 (3.4)	9.4 (2.8)	4.7 (2.3)
	10	25.8 (5.2)	20.3 (4.3)	16.7 (3.6)	13.1 (3.0)	9.7 (2.5)	6.7 (2.1)	3.0 (1.7)
	15	22.4 (4.0)	17.0 (3.3)	13.3 (2.8)	9.9 (2.3)	6.8 (1.9)	4.4 (1.6)	
Males	0	23.1 (13.1)	19.2 (10.4)	16.9 (8.3)	14.3 (6.7)	11.7 (5.3)	9.1 (4.3)	4.8 (3.4)
	1	24.8 (10.4)	20.4 (8.4)	17.7 (6.6)	14.8 (5.4)	12.0 (4.2)	9.2 (3.4)	4.9 (2.7)
	5	24.2 (7.3)	19.4 (5.8)	16.3 (4.7)	13.3 (3.7)	10.3 (3.0)	7.6 (2.4)	3.8 (1.9)
	10	21.5 (5.5)	16.6 (4.4)	13.5 (3.5)	10.5 (2.8)	7.7 (2.2)	5.3 (1.8)	2.5 (1.4)
	15	18.5 (4.1)	13.7 (3.3)	10.7 (2.6)	7.8 (2.1)	5.4 (1.7)	3.6 (1.3)	
Overall	0	27.3 (11.0)	22.3 (9.4)	19.1 (8.1)	16.0 (6.9)	12.9 (5.8)	10.0 (4.8)	5.4 (3.8)
	1	28.3 (9.1)	23.1 (7.7)	19.7 (6.7)	16.3 (5.7)	13.1 (4.8)	10.1 (4.0)	5.5 (3.2)
	5	27.4 (6.2)	21.9 (5.3)	18.1 (4.7)	14.6 (4.1)	11.3 (3.5)	8.2 (2.9)	4.2 (2.3)
	10	24.6 (4.4)	19.1 (3.8)	15.4 (3.3)	11.8 (3.0)	8.6 (2.5)	5.9 (2.1)	2.7 (1.7)
	15	21.3 (3.3)	15.9 (2.8)	12.3 (2.5)	9.0 (2.1)	6.2 (1.9)	4.0 (1.5)	

during the first years after diagnosis was more marked and appeared in all diagnosis cohorts. Finally, the patients' curves of the different age at diagnosis cohorts were closer to each other compared to women, a consequence of the lower variability of 10-year RS by age at diagnosis (Supplementary material Table 2). The LEs of cancer patients irrespective of sex were closer to those for females of younger ages and tended to approach those for males of increasing ages, mostly attributable to the different age patterns of breast and prostate cancer incidence. However, the population LE for the two sexes combined remained approximately in the middle of the sex-specific LEs. This led the YLL for both sexes to remain higher than the overall YLL, in which females were over-represented. For older ages at diagnosis, the YLL of males and females became close to each other, with the overall YLL remaining between the two.

Cancer-specific patterns

Beyond the differences between women and men, the LE initial drop (for example, YLL > 2) at diagnosis was observed at each and every different anatomical site considered, except for thyroid in females and thyroid up to age 37 years and melanoma and prostate for older patients in males. The LE pattern was mainly driven by the balance between all-causes and cancer mortality. The latter had a large impact on the youngest ages and decreased with increasing age at diagnosis and time since diagnosis (Figs. 1 and 2). Due to the LE indicator, two groups of tumours with different patterns were identified. The first group was characterised by an initial drop in the patients' LE followed by an increase in the first years after diagnosis and by a subsequent decrease, as for all cancers combined; the second group showed no increase after the initial LE drop but a regular decrease thereafter, sometimes following a short plateau (Figs. 1 and 2). The first group included the considered digestive (stomach, colon, and rectum) and respiratory cancers (lung and male larynx), cervix uteri, ovary, kidney, and leukaemia (Supplementary material Figs. A and B). This was a heterogeneous group; patients' LE when diagnosed at 45 years old ranked from approximately 29.6 (cervix uteri) to 6.5 (lung male), and patients' LE after 15 years since diagnosis (attained age = 60 years) ranked from 24.7 (stomach female) to 16.3 (lung male) (Supplementary material Tables 3 and 4). The second group also included all analysed cancers for young patients (Hodgkin lymphoma, testicular, and thyroid cancer) in addition to bladder, non-Hodgkin lymphoma (NHL), melanoma, breast, prostate, and

corpus uteri (Supplementary material Figs. A and B). Patients' LE when diagnosed at 45 years old ranked from approximately 38.8 (thyroid female) to 25.3 (NHL male) and patients' LE after 15 years since diagnosis (attained age = 60 years) ranked from 25.6 (thyroid female) to 15.8 (thyroid male) (Supplementary material Tables 3 and 4). The YLL indicator at age 45 years was particularly high for lung cancer (24.5 in women and 29.6 in men), ovarian cancer (22.7), and stomach cancer (19.0 in women and 17.6 in men). The lowest YLL at age 45 years was estimated for the cancers defined in the second group such as thyroid cancer in women (1.7) and melanoma in men (5.9) (Supplementary material Tables 3 and 4). After 15 years since diagnosis, YLL for patients diagnosed with digestive cancers, cervix and corpus uteri, prostate, and thyroid cancers became less than two years for all or almost all age classes at diagnosis. The YLL trend over time since diagnosis was ever decreasing with different speeds according to the lethality of the cancer type and the age at diagnosis.

After some years since diagnosis, all LE curves tended to overlap each other and most converged to the population values. In the long term, the patients' loss of LE with respect to the general population depended only on the attained age. At an attained age of 80 years, for example, LE of breast cancer patients varied very little (from 7.1 in women diagnosed at age 80 years to 8.7 in those diagnosed at age 45 years), both not very far from the LE of 10 estimated in cancer-free women of the same age (Fig. 1).

Discussion

The greatest difference in the patients' LE with respect to the sex- and age-matched general population was observed immediately after cancer diagnosis for each age class and analysed cancer due to the rapidly lethal course of the most aggressive cases. This initial difference was the highest for the youngest patients and progressively decreased with age at diagnosis, as young patients–although they generally have better cancer prognosis than older patients–had much lower mortality risks for non-cancer related causes. With increasing time since diagnosis, two different scenarios emerged. For more lethal cancers, patients' LE tended to increase during the first three to five years immediately after diagnosis. Indeed, the prognosis for survivors improved with each additional year survived, with the largest improvement in the first years after diagnosis. Patients' LE with less aggressive cancers did not show the same behaviour, as was the case for melanoma, bladder cancer, and

NHL in both sexes; and breast, corpus uteri, and thyroid for females and prostate, testis, and leukaemias for males.

YLL over time since diagnosis can be also interpreted as a measure of how close from being cured long-term survivors can be considered. For example, a proposed YLL cut-off of less than two years [10] could be defined as a threshold for cure in male colon cancer patients at nine years after diagnosis, when it occurred at age 45 years and three years after diagnosis at age 72 years. The identification of persisting YLL after many years since diagnosis was also consistent with other research [10,15]. A small but persisting patient excess risk in the cured patients with respect to the general population caused by factors linked with the cancer but that were not the cancer itself was described in a previous study [15]. This loss of lifetime can be attributed to second cancers, mostly for breast and testicular cancer [16,17], side effects of treatments, or to common risk factors shared with other diseases (for example, smoking and diet); therefore, the condition of reaching the same mortality risk of the general population may be too stringent to define the time to cure.

The results presented herein can be compared with those obtained from the data from the US for the period 2010–2012 [10]. The general population's LE was one to two years higher in Italy than in the US, and this was also reflected in the patients' LE. Taking this into account, YLL was approximately one year lower in the US than in Italian women diagnosed with colon and breast cancers (the greater difference was detected for breast cancer diagnosed at age 55–59 years, 4.6 vs 7, and after 15 years since diagnosis, 1 vs 3), while YLL was one to two years higher for men diagnosed with colon cancer in the US. This could be explained by their lower long-term RS, for example, 10-year RSs in 60–64 and 55–59-year-old patients in Italy were respectively 68% and 72% (Supplementary material Table 2) and approximately 61% and 63% in the US [18]. Other studies have estimated LE only at diagnosis using a cohort approach. Andersson et al. [5] used a flexible parametric model to estimate LE in a cohort of Swedish patients diagnosed with four cancer types in 1961–1970. Hakama et al. [19] analysed Finnish breast cancer data from 1956 to 1970. In both papers, a lower LE was estimated at diagnosis compared to Italian data. These differences can be attributable to the cohort approach and to the consequential use of less recent data to estimate the survival experience of patients in the first period after diagnosis and also to differences in country-specific LE of the general population.

Taking advantage of data with 23 years of follow-up, the excess hazard of patients diagnosed since 23 years or more was assumed to remain asymptotically constant at the value observed around 2010 and estimated by moving averages. Other methods can be used for extrapolating survival beyond the available follow-up time. Hakama et al. [19] assumed excess mortality to reach zero (statistical cure) or to stabilise to a constant. Andersson et al. [5] used a flexible parametric model and Fang et al. [20] used a semi-parametric distribution for survival. Nonetheless, a non-parametric estimation method was preferred as it is simpler and free from model specifications and other parametric assumptions. By prioritising the use of information from the latest follow-up years, the period approach provides more reliable predictions than the cohort method, which does not provide sufficient follow-up for more recently diagnosed patients. Despite these advantages, the LE estimates of patients diagnosed before 2011 can change in future scenarios, as the prognosis of many cancers is ever improving [8]. Unfortunately, in this database, the information on cancer stage, cancer treatment, lifestyle, and socio-economic status was not available, although it also plays an important role in determining cancer patients' LE [9].

A limitation was related to the representativeness of the present results at the national level, as the long-established cancer registries contributing to this study covered only 10% of Italy. Variability of LE across regions cannot be excluded, although the cancer registries were well distributed across all Italian areas [8]. The generalisation of the results herein presented to other countries requires caution albeit the Italian survival levels were similar to those of most central and southern European countries [21].

For cancer patients, the consideration of quality of life is also very important, even more so than the length of life itself [11], but unfortunately this indicator could not be retrieved from population-based cancer registries.

Survivorship care is an important research topic [22]; country-specific detailed estimates and projections of the numbers of persons living after different cancer diagnoses [23], cancer cure [24], time to cure [25], and "real-word" estimates of the impact of cancer on specific populations are particularly relevant to policy makers. Changes in LE during the course of the disease can provide a different and complementary point of view in investigating cancer cures with respect to the RS-based criteria, providing helpful information of the lifetime impact of a cancer diagnosis.

Conclusions

Providing quantitative data is essential to better define clinical follow-up, plan health care resources allocation, and optimal long-term cancer surveillance. The longer the time since diagnosis, the higher the impact of other factors, in addition to the tumour itself, on cancer survivors' duration (and quality) of life. These "real-world" indicators are easily understandable, and therefore, they become useful measures to be adopted in the clinician-patient communication, especially after many years since diagnosis.

Conflict of Interest

The authors have declared no conflict of interest.

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Role of funding source

Ethical approval and consent to participate

Not applicable.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jare.2019.07.002.

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