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Original Contribution

Indicators of cure for women living after uterine and ovarian cancers: a population-based study

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Abstract

This study aims to estimate long-term survival, cancer prevalence, and several cure indicators for Italian women with gynecological cancers. Thirty-one cancer registries, representing 47% of the Italian female population, were included. Mixture cure models were used to estimate net survival, cure fraction, time to cure (when 5-year conditional net survival becomes > 95%), cure prevalence (women

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who will not die of cancer), and already cured (living longer than time to cure). In 2018, 0.4% (121 704) of Italian women were alive after diagnosis of corpus uteri cancer, 0.2% (52 551) after cervical cancer, and 0.2% (52 153) after ovarian cancer. More than 90% of patients with uterine cancers and 83% with ovarian cancer will not die from their neoplasm (cure prevalence). Women with gynecological cancers have a residual excess risk of death <5% at 5 years after diagnosis. The cure fraction was 69% for corpus uteri, 32% for ovarian, and 58% for cervical cancer patients. Time to cure was ≤10 years for women with gynecological cancers aged <55 years; 74% of patients with cervical cancer, 63% with corpus uteri cancer, and 55% with ovarian cancer were already cured. These results can contribute to improving follow-up programs for women with gynecological cancers and supporting efforts against discrimination of already cured ones.

This article is part of a Special Collection on Gynecological Cancers.

Key words: cure fraction; time to cure; cancer prevalence; ovarian cancer; cervical cancer; corpus uteri cancer; long-term survival; mixture cure models.

Introduction

Cancers of the cervix, corpus uteri, and ovary represent the vast majority of gynecological cancers worldwide, with an annual incidence of more than 1.3 million cases (respectively, 6.5%, 4.5%, and 3.4% of all new cancer cases in women) and mortality exceeding 650 000 deaths.[1] These cancers represent a major global burden also in Italy with approximately 10 000 new cases per year of corpus uteri, 5400 of ovarian, and 3200 of cervical cancers, ie, approximately 10% of all neoplasms diagnosed in women. For these tumors, estimated deaths per year in Italy are approximately 5200 (3200 for ovarian cancer). An incidence-to-mortality ratio >3.5 of gynecological cancers accounts for the estimates of 207 820 Italian women (684/100 000) alive in 2010 after a diagnosis of one of these cancers.[2] Notably, this number is more than 10 times higher than the annual number of incident cases and represents nearly 15% of all Italian women living after cancer diagnosis. The number of prevalent patients is expected to grow due to the combined effect of early diagnosis and advances in treatment that have caused the mortality rates to decrease in recent years, thus increasing the number of long-term gynecological cancer survivors (ie, those alive >5 years after diagnosis).[3-5]

Several studies have explored in Italy[6,7] and elsewhere[8-10] the survival of women with gynecological cancers. However, to the best of our knowledge, few population-based studies focused on cure indicators such as cure fraction and time to cure for these cancers.[11-19]

The present study aims to provide estimates of complete cancer prevalence and indicators of cancer cure for Italian patients with uterine and ovarian cancers.

Methods

The methodological details on the study population, definitions, models used and assumptions, and their validation can be found in a recent paper.[20] This study included 31 population-based Italian cancer registries (CRs) with at least 9 years of registration and patient vital status ascertainment at least 1 year after the last incidence date (ie, December 31, 2017). The registration period ranged from 9 to 40 years, with a median of 22 years. At the end of 2017, these 31 CRs covered more than 14.5 million women, representing 47% of the Italian female population. Using the *International Statistical Classification of Disease and Related Health Problems, Tenth Revision* (ICD-10),[21] women were identified who had the following malignant gynecological cancers: invasive cervical cancer (C53, cervix uteri), corpus uteri cancer (C54), and ovarian cancer (C56).

As of January 1, 2018, 146 678 incident malignant gynecological cancers were diagnosed in Italian women living in the areas covered by the 31 participating cancer registries (Table S1): 72 447 corpus uteri (> 90% endometrial), 48 829 ovarian, and 25 402 cervical cancers. They represent 87% of all gynecological cancers (C51-C58) diagnosed in Italy in the study period.

The mean age at diagnosis was 65 years for corpus uteri, 64 for ovarian, and 57 for cervical cancer. Approximately 80% of the patients with corpus uteri cancer and 70% with ovarian cancer were diagnosed after 54 years of age while cervical cancer was diagnosed at younger ages (48% aged <55 years). These cases were included to calculate the complete prevalence of gynecological cancer. To estimate cancer-specific prevalence, we considered the individual's first primary tumor matching the selected cancer site. Model-based long-term survival and cure indicators were estimated using a subset of 22 CRs with at least 15 years of registration (for a coverage of 30% of the Italian population).

Net survival (NS) is the probability that cancer patients survive their cancer up to a given time since diagnosis, after controlling for competing causes of death. NS makes it possible to compare populations, with the assumption that the disease under investigation was the only possible cause of death. NS was calculated for cases of all ages diagnosed in 1991-2017 and followed up until the end of 2018, using the cohort method and the Pohar Perme approach, as implemented by SEER*Stat software.[22] Model-based NS was calculated using mixture cure models as a combination of 2 models that estimate both the cure fraction (CF)—ie, the proportion of cured patients reaching the same death rates as the general population—and the survival function of the remaining "not-cured" patients (ie, fatal cases, 1 − CF). Five-year conditional net survival (CNS) was calculated as the probability of surviving 5 additional years, given that patients already survived a certain number of years.

The cure fraction (CF) is the proportion of newly diagnosed cases who will not die of cancer (ie, "cured patients"), calculated by the mixture-cure model as the NS value corresponding to the attained age of 100, used here as the maximum reasonable age a patient can reach. CF was calculated for patients diagnosed in 2000 and 2010.

The time to cure (TTC) is defined as the time to reach a 5-year CNS >95%. TTC was centered on 2010 as the year of diagnosis, approximately the median year of diagnosis for Italian gynecological cancer women prevalent in 2018.

The complete prevalence represents all previously diagnosed cancer survivors, regardless of the time elapsed since diagnosis, and was calculated as of January 1, 2018, by adjusting the observed prevalence in each registry using the completeness index method. The absolute number of prevalent cases in Italy was obtained as the sum of proportions calculated by pooling cancer registries, multiplied by the corresponding Italian population.

The cure prevalence (CurePrev) is the proportion of all prevalent patients who will not die of cancer. CurePrev was also calculated separately for prevalent patients who have already survived at least 5, 10, and 15 years after their cancer diagnosis and the complement of this quantity (ie, 1 − CurePrev) can be interpreted as their residual excess risk of death (ie, those who are expected to die because of cancer).

Table 1. Complete prevalence[a] (cases and proportion per 100 000 women) for gynecological cancer patients by site and age at prevalence, Italy, 2018.

Cancer site	No. of prevalent cases	Proportion per 100 000 women by attained age, years					
		All ages	0-44	45-54	55-64	65-74	≥75
Cervix uteri	52 551	171	28	169	270	312	434
Corpus uteri	121 704	395	11	148	497	1072	1312
Ovary	52 153	169	25	147	272	391	396

[a]The absolute number of prevalent cases in Italy was calculated as the sum of proportions of prevalence estimates (age- and site-specific, obtained pooling cancer registries in the north-central area and the South-Islands included in this study) multiplied by the corresponding Italian population in the same areas at the index date.

The already cured are the number and proportion of all prevalent patients who live longer than the TTC. Already cured patients in 2018 were estimated as the sum by age of patients living longer than TTC.

According to Italian legislation (see Acknowledgments for details), population-based cancer registries collect pseudonymized personal data for surveillance purposes that do not need the collection of explicit individual consent, without any direct or indirect intervention on patients; therefore, the approval of a research ethics committee was not required.

Results

The 10-year NS of women diagnosed with gynecological cancers in Italy between 1991 and 2008, by cancer site and age group, are presented in Figure S1. For cervical cancer patients diagnosed at ages <65 years, the 10-year NS increased from 1991-1993 to 2006-2008 by approximately 5 percentage points, and was stable for women diagnosed at older ages. In the most recent period (2006-2008), women aged up to 45 years reached the highest NS (82%) compared with the older age groups (71% ages 45-54, 62% ages 55-64), while 10-year NS were more than 10 percentage points lower for women aged 65 years or older.

For corpus uteri cancer patients aged ≥55 years, there was an increase of about 5 percentage points, whereas no improvement was observed for those diagnosed at 45-54 years. For patients aged <65 years in 2006-2008, the 10-year NS was >80%, 72% at ages 65-74, and 55% for those aged ≥75 years.

Women with ovarian cancer have the lowest survival levels compared with patients with other gynecological cancers but saw major increases in the period of observation. The 10-year NS rose by approximately 10 percentage points from 1991-1993 to 2006-2008 for women aged between 45 and 74 years, remaining substantially stable for younger (<45) and older (≥75) women.

Table 1 shows the complete prevalence, in terms of the number of cases and proportions per 100 000, as of January 1, 2018, of women diagnosed with gynecological cancer in Italy by cancer site and age group. Figure S2 presents the corresponding distribution of prevalent cases by time from diagnosis.

Overall, 52 551 women were alive in Italy in 2018 after a cervical cancer diagnosis, corresponding to a prevalence proportion of 171 per 100 000 (0.2% of the whole female population). The prevalence was higher than for other gynecological cancers among younger women (<55 years). Only 17% of cervical cancer patients had a diagnosis in the previous 5 years and 68% in the previous >10 years.

Persons living after corpus uteri cancer were 121 704 (395 per 100 000 women, 0.4% of the Italian female population), with a steep increase with age (prevalence >1% of all women aged 65 years or older). The proportion of corpus uteri cancer patients alive more than 5 years after diagnosis was 72%, and 50% after >10 years.

In 2018, 52 153 Italian women were alive after ovarian cancer, which amounts to a proportion of 169 per 100 000 (0.2% of all Italian women, nearly 0.4% at ages 65 or more); 71% and 55% of all prevalent cases live longer than 5 years and 10 years after diagnosis, respectively.

Figure 1 illustrates the cure fraction of women diagnosed with gynecological cancer in Italy, in 2000 and 2010, respectively, by cancer site and age group.

For women diagnosed in 2010 with cervical cancer, the CF was 58% in all ages combined, spanning from more than 70% below the age of 55 years to 55% in women aged 55-64 years. Of note, in women who were not in the screening group (age ≥65), the CF was about 20-30 percentage points lower compared with women in the age group targeted for the screening (55-64 ages). Also, CF has slightly improved (3-5 percentage points) between 2000 and 2010 only for cases below the age of 65 years.

The CF was 69% for all women diagnosed with corpus uteri cancer in 2010 with a 2-percentage-point increase compared with those diagnosed in 2000. CF was >80% for women diagnosed in 2010 at before age 55 years, 76% at 55-64 years, and 67% at 65-74 years.

The CF of women diagnosed with ovarian cancer in 2010 was 32% for all ages combined (half that for the other gynecological cancers) with a 4-percentage-point increase in comparison with women diagnosed in 2000. As with survival, CF decreased dramatically when age increased: from 50% at age 45-54 years to 38% at 55-64 years and 27% at 65-74 years.

The number of prevalent patients with gynecological cancers who had the same life expectancy as their peers in Italy on January 1, 2018, is presented in Table 2 and Figure 2. Table 2 shows the cure prevalence in terms of absolute number and percentage by cancer site and years since diagnosis; Figure 2 shows the cure prevalence in terms of proportions per 100 000 by cancer site and years since diagnosis.

Among women who had cervical cancer, 93.1% (48 911 patients) will not die of their cancer, and 97.5% of those who already survived ≥5 years will not die of their cancer, with a residual proportion of death of <2% for those who survived ≥10 years. Among women living in 2018 after corpus uteri cancer, 91.3% (111 099) will not die as a result of their cancer. Cure prevalence becomes 95.9% for women diagnosed ≥5 years before and 97.6% for those alive 10 years or more after diagnosis (ie, the residual proportion of deaths due to corpus uteri cancer was 4.1% for those alive ≥5 years and 2.4% for those ≥10 years after diagnosis).

Cure prevalence was 83.4% (43 484) among women living after ovarian cancer (lower than for other gynecological cancers) but

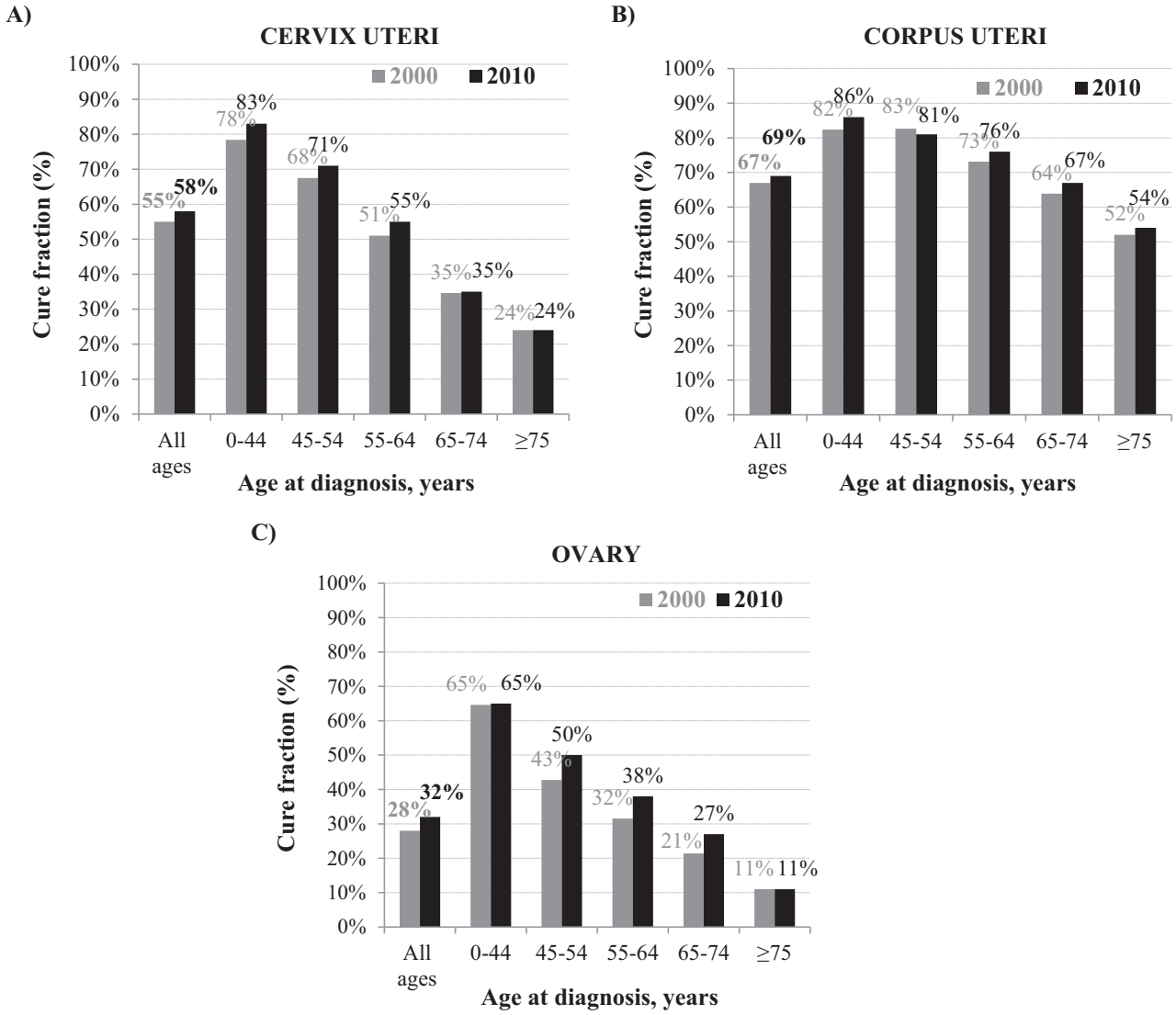

Figure 1. Cure fraction (%) for gynecological cancer patients diagnosed in Italy in 2000 and 2010 by site and age at diagnosis. Cure fraction was estimated as net survival until age 100 years. Estimates for all age groups were calculated as the average of age-specific cure fractions, weighted by the proportion of incident cases in the corresponding age group.

the residual proportion of death decreased to 3.8% for those alive ≥5 years after diagnosis and to less than 1% for those alive 10 years or more after diagnosis.

Table 3 shows the TTC of women diagnosed with gynecological cancers in Italy, by cancer site and age at diagnosis, and those that were already cured, by cancer site at all ages combined; Figure S3 shows the corresponding numbers and percentages of the already cured by cancer site and age group.

TTC of women with cervical cancer was reached at approximately 5 years at younger ages (<55 years, representing half of the incident cases, Table S1). For women aged 65 years or older, an excess risk of death remains after 10 years of follow-up (ie, TTC of >10). As a result, the majority of prevalent cervix uteri cancer patients have already reached TTC and can be considered as already cured (74%, 38 993). Notice that 20% of those already cured after cervical cancer are aged <55 years.

Table 2. Cure prevalence[a] for gynecological cancer patients by site and years since diagnosis, Italy, 2018.

Cancer site	Cure prevalence among patients alive since							
	≥0 years		≥5 years		≥10 years		≥15 years	
	No.	%	No.	%	No.	%	No.	%
Cervix uteri	48 911	93.1	42 406	97.5	34 983	98.6	28 758	99.5
Corpus uteri	111 099	91.3	83 999	95.9	59 319	97.6	39 414	98.8
Ovary	43 484	83.4	35 532	96.2	28 186	99.1	21 736	99.8

[a]Number and percentage of prevalent cases on January 1, 2018, who had the same life expectancy as their peers in the general population among those alive more than 0 (ie, all prevalent cases), 5, 10, or 15 years after diagnosis. The complement of these proportions (ie, 1 − cure prevalence) can be read as the residual excess risk of death.

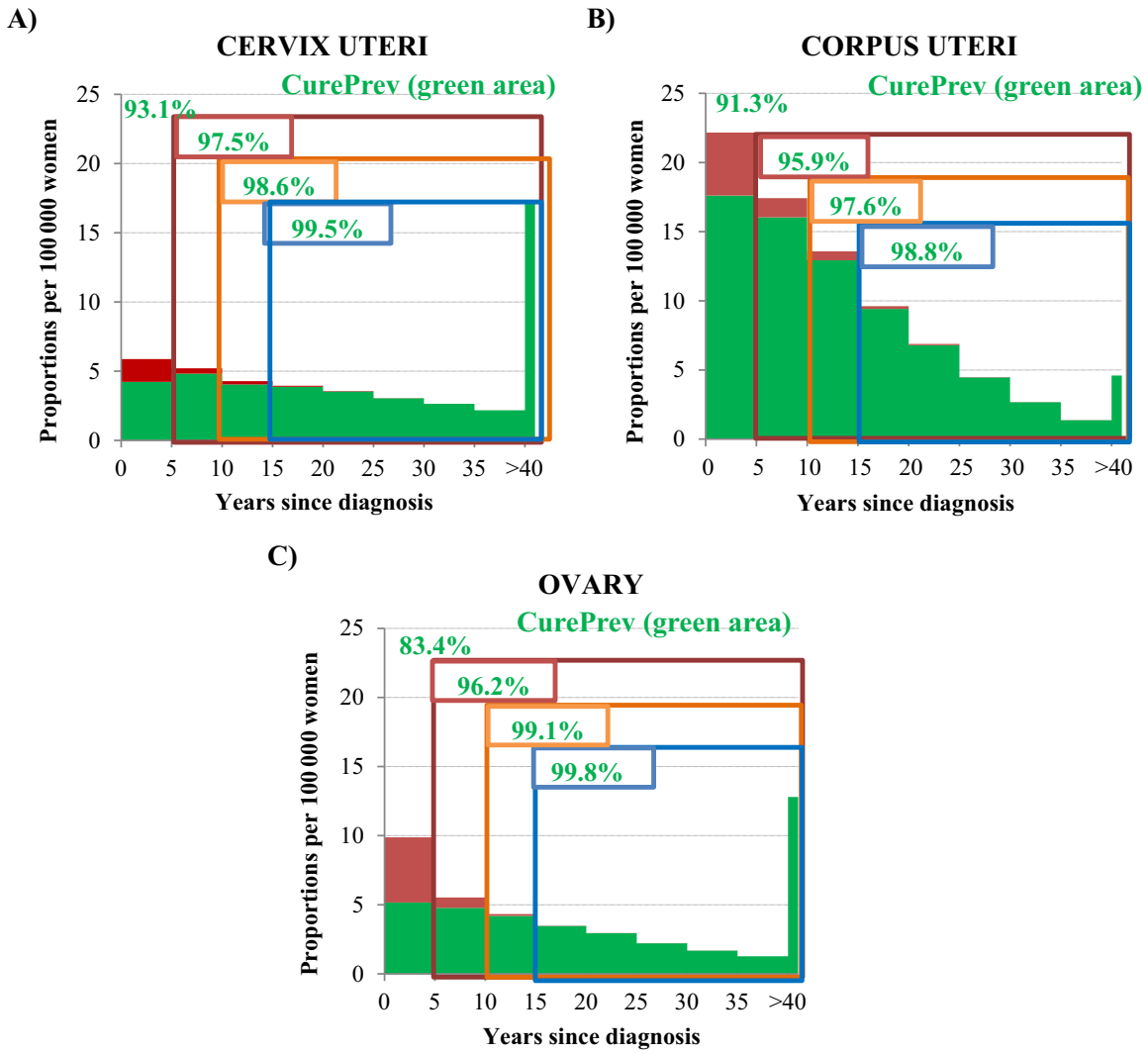

Figure 2. Cure prevalence (CurePrev) for gynecological cancer patients by site and years since diagnosis. Italy, 2018. Each bar of the figure represents the proportions of prevalent cases per 100 000 women by time since diagnosis in 5-year periods, at all ages as of January 1, 2018. For each time interval, the green part of the bars indicates the women who have the same life expectancy as their peers in the general population. The cure prevalence is the proportion of these women, expected not to die as a result of their cancer, out of the total prevalent cases (ie, 91.3% for corpus uteri cancer, all ages). Focusing on patients alive more than 5, 10, or 15 years after diagnosis (included in the red, orange, and blue boxes, respectively), the cure prevalence is the probability of being cured, conditioned to survive at least 5, 10, or 15 years after diagnosis. The complement of these probabilities (ie, 1 – CurePrev) can be read as a residual excess risk of death.

TTC was <10 years in all age groups for women with cancer of the corpus uteri, and 63% of all prevalent patients (corresponding to 76 431 women) can be considered as already cured since they have already reached TTC. More than 80% of these women (61 265) are aged ≥65 years.

TTC was approximately 10 years in the age groups between 45 and 74 years for women with ovarian cancer, and 55% of prevalent ovarian cancer patients were estimated to be already cured. These numbered 28 475 women and, of them, 19 048 were aged 65 years or older.

Table 3. Time to cure[a] and already cured[b] for gynecological cancer patients by site and age at diagnosis in Italy, 2018.

Cancer site	TTC, years, by age at diagnosis, years					Already cured, all ages	
	≤44	45-54	55-64	65-74	≥75	%	No. of cases
Cervix uteri	4	6	12	>15	12	74	38 993
Corpus uteri	4	5	7	9	7	63	76 431
Ovary	8	10	11	11	>15	55	28 475

Abbreviation: TTC, time to cure.
[a]TTC was calculated for women diagnosed in 2010 as the time to reach a 5-year conditional net survival of more than 95%, for each cancer site and age.
[b]Calculated as the number and proportion of prevalent women in 2018 who already reached the site- and age-at-diagnosis–specific TTC. If TTC > 15 years, prevalent cases were never considered already cured.

Discussion

In 2018, more than 226 000 women were living in Italy after a gynecological cancer diagnosis, corresponding to 0.74% of the female population, and the large majority of them will be cured of their malignancy (ie, >90% for uterine cancer patients, 83% for ovarian cancer patients). This study identified a time to cure of <10 years for all women with cancer of the corpus uteri and cervical cancer aged <55 years, and <12 years for ovarian cancer patients aged <75 years. As a consequence, 144 000 Italian women living longer than time to cure after a diagnosis of gynecological cancer are estimated to be already cured. They represent 65% of all prevalent gynecological cases: 74% are women with cervical cancer, 63% with cancer of the corpus uteri, and 55% with ovarian cancer. According to our results, the improvement in survival of gynecological cancer patients was estimated also in terms of cure fraction increasing between 2000 and 2010 by more than 5 percentage points among women with ovarian cancer aged 45-74, and about 2-3 percentage points among women with uterine cancers.

Cervical cancer

Over the last two decades, a modest survival increase has been a common observation in several high-income countries.[6,9,23] For Italian women diagnosed in 2010 with cervical cancer under the age of 55, we found a probability of cure >70% with values falling to 35% or below after the screening ages. Similar results were provided by other authors in Europe[13,14,16] and elsewhere.[17,19] Since treatment options were substantially unchanged between the 1990s and 2010s,[24] the chances of cure of cervical cancer depend largely on the extent of disease involvement at the time of diagnosis, that is, the patient's screening experience.[12,25] In Italy, the gradual implementation of regional screening programs between the 1990s and 2010s has resulted in a decreased incidence of invasive cancers with no substantial change in stage distribution except for a within-stage shift.[26] In addition, the poor sensitivity of the Papanicolaou test for preinvasive, as well as early invasive, glandular lesions, has brought an increasing proportion of adenocarcinoma cases out of total incidence[27] and, among these, a greater proportion of advanced-stage diseases compared with squamous cell carcinomas.[28] While it is unlikely that the implementation of Papanicolaou test screening will further improve the probability of cure and survival of patients with invasive cervical cancer, more sensitive human papillomavirus DNA testing has the potential to further reduce incidence and mortality.[29]

Notably, cure indicators after cervical cancer in women over 64 years (ie, age of cessation of screening) suffer from a much more marked reduction in cancer survival in comparison with other gynecological cancers.[7] This suggests that, among older women, invitations to organized screening activities are not replaced by a spontaneous decision to seek gynecological care in the private setting. The barriers most likely to exert a negative effect are increased embarrassment, fear and shame, anxiety about the test procedure, and sexual inactivity,[30] coupled with limited knowledge and understanding of the causes of cervical cancer.[31] In particular, elderly women may erroneously feel they are at low risk for cervical cancer because of their current sexual inactivity. Mass communication should stress that cervical screening is important for women ≥65 years old with no or little screening history.

Cancer of the corpus uteri

Women living after cancer of the corpus uteri represent more than half of all gynecological prevalent patients (0.4% of all women in Italy), with a cure fraction for incident cases of 69%, thus confirming the relatively good prognosis of this cancer type.[13,14,16,17,19,32] Survival and cure fraction of corpus uteri cancer in Italy has increased little (2% between 2000 and 2010), similar to other studies that have reported almost stable survival percentages[6,23] and poorer improvements in younger women.[33] Although most patients with cancer of the corpus uteri have a low risk of recurrence and are treated with surgery alone,[34] we found a residual risk of death for patients alive 5 years or more after diagnosis (ie, 4.1%) slightly higher than for other gynecological cancer.[35] This is probably due to factors related to the incidence of cancer of the corpus uteri (ie, overweight/obesity, diabetes, and hypertension)[36] that also correlate with a poor prognosis.

Ovarian cancer

Ovarian cancer remains a malignancy with a severe prognosis[6,9,37] due to a lack of effective screening methods and less specific clinical symptoms (most of the patients are diagnosed at an advanced stage), with a cure fraction of approximately one-third of patients as reported in our findings and similar population-based studies.[14-17,19,38] Nevertheless, survival and cure fraction from ovarian cancer in Italy has increased to an appreciable extent (4 percentage points from 2000 to 2010), especially in middle age groups (ie, 45-74 years). TTC was reached after 11 years, as in similar studies in France[14] or South Korea,[39] with a small (<1%) excess risk of mortality compared with the general population for patients alive 10 years or more after diagnosis (Figure 2C).

These findings are of considerable interest and novelty. At variance with ours, some previous studies have shown that, while treatment benefits for some common malignancies derived primarily from increases in cure fraction, the survival gain for ovarian cancer may be obtained despite persisting or recurrent disease, that is, by prolonging the life expectancy of women with cancer recurrence or an incurable condition (due to newly available drugs or improvements in supportive care instruments) and not with a true increase in the cure rate,[40] in analogy with what has been reported for breast cancer patients.

Strengths and limitations

The cure models used are capable of identifying how treatment advances have changed survival probabilities and, ultimately, mortality rates. The main strengths of this study include its population-based setting, which minimized the selection bias present in most hospital-based studies and clinical trials, the use of standardized registration procedures, and the long-term follow-up of vital status,[6,20] each contributing to the reliability of the estimation of long-term survival, prevalence, and cure indicators. Another strength of the study is a comprehensive description of several indicators of long-term survival, prevalence, and cure,[41] and the link between them.[20]

Among the limitations, we acknowledge that the present study, like most population-based studies, suffers from a lack of individual data on important prognostic factors such as stage of disease,[19,42,43] socioeconomic status, treatment,[44] and mode of diagnosis (screen-detected).[12] The inclusion of such variables in cure models would help to identify which subgroups of survivors still maintain the excess risk of death many years after cancer diagnosis and treatment, thus improving targeting the type and intensity of care that will be needed across various phases of survivorship.

There are also some methodological limitations. The lack of standardized methods for estimating cancer cure indicators[19,45,46] suggests the need for caution in the international comparisons

and interpretation of results for cancer cure indicators.[20] The reliability of net survival estimates used as input for cure models is limited for older age groups (eg, 75 years or older) due to a reduced number of cases and competing risks of death, and corresponding results should be interpreted with caution.[47] TTC is sensitive to the choice of the conditional survival threshold used to identify a low risk of recurrence, death, or the margin of clinical relevance. This is particularly the case for cancer types with a non-negligible long-term excess mortality rate, rarely observed for gynecological cancers.[16,45] Nevertheless, it should be noted that the methodology for calculating the cure indicators presented in our study (in particular CF and TTC) is reproducible and feasible.[48]

Relevance for patients and oncologists

These findings strongly support the concept that cancer cure is a realistic expectation for women with gynecological cancers and are of noteworthy practical interest.[49,50] The population living after gynecological and other types of cancer is increasing and represents a substantial burden on the health care system.[51] It is hoped that these results will help design updated follow-up programs, the reduction of medicalization, and a better focus on the management of late effects.[52] Finally, we believe these results may help clinicians to implement a personalized follow-up that takes care of the concomitant diseases that affect women cured of cancer and to improve their quality of life, avoiding the discrimination and financial toxicity experienced by cancer survivors[53] and, thus, supporting their full rehabilitation.

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Supplementary material

Supplementary material is available at *American Journal of Epidemiology* online.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Disclaimer

The funding sources had no involvement in the study design, in the collection, analysis, and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.

Data availability

All data relevant to the study are included in the article or uploaded as supplementary information. Research data (aggregate) are available from the corresponding authors upon reasonable request.

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