Cancer Epidemiology 60 (2019) 93–101

Contents lists available at ScienceDirect

Cancer Epidemiology

journal homepage: www.elsevier.com/locate/canep

Time-to-cure and cure proportion in solid cancers in France. A population based study

Gaëlle Romain[a,b,c,d], Olayidé Boussari[a,c,d,e], Nadine Bossard[f,g,h,i], Laurent Remontet[f,g,h,i], Anne-Marie Bouvier[a,b,c,d], Morgane Mounier[b,c,d,j], Jean Iwaz[f,g,h,i], Marc Colonna[k], Valérie Jooste[a,b,c,d,*], French Network of Cancer Registries (FRANCIM)[1]

[a] Registre Bourguignon des Cancers Digestifs, Dijon, France
[b] Centre Hospitalier Universitaire de Dijon Bourgogne, Dijon, France
[c] INSERM, LNC UMR1231, Dijon, France
[d] Université de Bourgogne Franche-Comté, Dijon, France
[e] Laboratoire d'Excellence LabEX LipSTIC, ANR-11-LABX-0021, Dijon, France
[f] Hospices Civils de Lyon, Service de Biostatistique-Bioinformatique, Lyon, France
[g] Université de Lyon, Lyon, France
[h] Université Lyon 1, Villeurbanne, France
[i] CNRS UMR 5558, Laboratoire de Biométrie et Biologie Évolutive, Équipe Biostatistique Santé, Pierre-Bénite, France
[j] Registre des Hémopathies Malignes de Côte d'Or, Dijon, France
[k] Registre du Cancer de l'Isère, Centre Hospitalier Universitaire Grenoble-Alpes, Grenoble, France

ARTICLE INFO

Keywords:
Statistical cure
Time-to-cure
Cure proportion
Cure models
Population based cancer registry
Survival
Epidemiology

ABSTRACT

Background: In cancer care, the cure proportion (P) and time-to-cure (TTC) are important indicators for practitioners, patients, and healthcare policy makers. The recent definition of TTC as the time at which the probability of belonging to the cured group reaches 95% was used for the first time.
Methods: The data stem from the common database of French cancer registries including 335,358 solid tumours diagnosed between 1995 and 2009 at 27 sites. P and TTC were estimated through a flexible parametric net survival cure model for each cancer site, sex, and age at diagnosis with acceptable assumption of cure (excess mortality rate ≤ 0.05).
Results: TTC was ≤ 5 years and P was $> 80\%$ for skin melanoma and thyroid and testis cancers. It was 0 for testis cancer in men < 55 and for thyroid cancer in men < 45 and women < 65. TTC was between 5 and 10 years for all digestive cancers except small intestine and all gynaecologic cancers except breast. It was ≥ 10 years in prostate, breast, and urinary tract. The range of P according to age and sex was 37–79% for urinary tract 72–88% for prostate and breast, 4–16% for pancreatic and 47–62% for colorectal cancer.
Conclusion: Time-to-cure was estimated for the first time from a large national database and individual probabilities of cure. It was 0 in the younger patients with testis or thyroid cancer and < 12 years in most cancer

* Corresponding author at: Registre Bourguignon des cancers digestifs, UFR des sciences de santé, BP 87900, F-21079, Dijon Cedex, France.
E-mail address: valerie.jooste@u-bourgogne.fr (V. Jooste).

[1] **French Network of Cancer Registries (FRANCIM):** Brice Amadeo (Registre des cancers de Gironde), Patrick Arveux (Registre des cancers du sein et des cancers gynécologiques de Côte-d'Or), Isabelle Baldi (Registre des tumeurs primitives du système nerveux de la Gironde), Simona Bara (Registre des cancers de la Manche), Anne- Marie Bouvier (Registre bourguignon des cancers digestifs), Véronique Bouvier (Registre des tumeurs digestives du Calvados), Jacqueline Clavel (Registre des hémopathies malignes de l'enfant), Marc Colonna (Registre du cancer de l'Isère), Gaëlle Coureau (Registre des cancers de Gironde), Anne Cowppli-Bony (Registre des tumeurs de Loire-Atlantique et Vendée), Tania Dalmeida (Registre général des cancers de Haute Vienne), Laetitia Daubisse-Marliac (Registre des cancers du Tarn), Gautier Defossez (Registre général des cancers de Poitou-Charentes), Patricia Delafosse (Registre du cancer de l'Isère), Jacqueline Deloumeaux (Registre général des cancers de Guadeloupe), Pascale Grosclaude (Registre des cancers du Tarn), Anne-Valérie Guizard (Registre général des tumeurs du Calvados), Clarisse Joachim (Registre général des cancers de Martinique), Brigitte Lacour (Registre National des Tumeurs Solides de l'Enfant), Bénédicte Lapôtre-Ledoux (Registre du cancer de la Somme), Emilie Marrer (Registre des cancers du Haut-Rhin), Marc Maynadié (Registre des hémopathies malignes de Côte d'Or), Florence Molinié (Registre des tumeurs de Loire-Atlantique et Vendée), Alain Monnereau (Registre des hémopathies malignes de la Gironde), Jean-Baptiste Nousbaum (Registre finistérien des tumeurs digestives), Juliette Plenet (Registre des Cancers de Guyane), Sandrine Plouvier (Registre général des cancers de Lille et de sa région),Camille Pouchieu (Registre des tumeurs primitives du système nerveux de la Gironde), Michel Robaszkiewicz (Registre finistérien des tumeurs digestives), Claire Schvartz (Registre des cancers thyroïdiens Marne-Ardennes), Brigitte Trétarre (Registre des tumeurs de l'Hérault), Xavier Troussard (Registre Régional des Hémopathies Malignes de Basse Normandie), Michel Velten (Registre des cancers du Bas-Rhin), Anne-Sophie Woronoff (Registre des tumeurs du Doubs et du Territoire de Belfort).

https://doi.org/10.1016/j.canep.2019.02.006
Received 3 September 2018; Received in revised form 21 January 2019; Accepted 7 February 2019
Available online 30 March 2019

sites. These results should help improve access to credit and insurance for patients still alive past the estimated TTCs.

1. Introduction

Of the three million people living in France with a personal history of cancer [1], a large proportion will not die from cancer. Although clinical cure is difficult to evaluate, especially in large cohorts, statistical cure can be defined as the absence of death due to cancer. The proportion that will not die from cancer is therefore the cure proportion P (or cure fraction). P can be estimated using net survival cure models and cancer registry data. Up to now, cure models provided estimations of the cure proportion and of the whole net survival of fatal cases [2,3]. The time-to-cure is also of great interest for public health deciders, epidemiologists, physicians, and patients. Only one previous study has provided estimations of the time-to-cure using conditional net survival applied to Italian cancer registries data [4]. Boussari et al. have recently proposed a more intuitive definition of the time-to-cure, as the delay TTC after which the probability of belonging to the cured group (estimated from the cure proportion and the net survival) reaches a high pre-defined value [5].

In cancer studies, net survival is defined as the survival that would be observed if cancer were the only cause of death [6,7]. In large cohorts, the causes of death are not reliable; net survival is thus estimated using the excess mortality rate; i.e., the difference between the mortality rate observed in the cohort and the mortality rate expected in the general population that shares same socio-demographic characteristics [8,9]. When cure occurs, the excess mortality rate tends to zero; thus the net survival tends to the cure proportion [10]. The ratio between the cure proportion and the net survival is then the probability of belonging to the cured group [5,11].

As a follow-up of our previous study which proposed TTC as a definition of the time-to-cure and using net survival cure models, the aim of the present study was to estimate the cure proportion and the time-to-cure in France regarding solid cancer sites for which the assumption of statistical cure was deemed acceptable.

2. Patients and methods

2.1. Patients and main characteristics

The study concerned all solid tumours diagnosed January 1, 1995 to December 31, 2009 in patients aged 15–74 years (N = 335,358) and

Table 1
Results of checking the assumption of cure by age-group at diagnosis in men.

Cancer site	Number at diagnosis	Number at 5 years	Number at 10 years	Number deaths[a]	Percentage of loss to follow-up[a]	15–44 years	45–54 years	55–64 years	65–74 years
Bones	405	236	199	219	3.2	C	C	C	NC
Central nervous system	2925	614	479	2475	1.1	NC	C	NC	NC
Choroid[b]	281	194	161	123	1.1	–	–	–	–
Colon[c]	16029	9206	7769	8803	2.1	C	C	C	C
Colon and Rectum	27861	15959	13279	15538	2.0	C	C	C	C
Head and neck	14137	4829	3317	11297	1.0	NC	NC	NC	NC
Kidney	6183	4149	3580	2840	2.0	C	C	C	C
Lip[b]	400	327	276	167	4.5	–	–	–	–
Lung	30072	4620	3371	27052	0.8	C	C	NC	NC
Malignant neoplasm without specification of site[b]	132	33	30	103	4.3	–	–	–	–
Nasopharynx[c]	339	177	141	206	3.5	C	C	C	NC
Oral cavity[c]	3211	1305	908	2430	1.2	NC	NC	NC	NC
Rectum[c]	11832	6753	5510	6735	1.9	C	C	C	C
Skin melanoma	4571	3804	3508	1158	4.3	C	C	C	C
Stomach	5460	1415	1153	4397	1.8	C	C	C	C
Testis	3021	2864	2826	226	3.7	C	C	C	C
Thyroid	2060	1808	1708	381	2.6	C	C	C	C
Tissue sarcoma	1168	669	593	607	2.0	C	C	C	C
Tongue[c]	2624	913	658	2051	1.2	C	NC	NC	NC
						15-54 years		55-64 years	65-74 years
Biliary tract	1095	235	184	930	0.8	C		C	C
Bladder	7972	4343	3500	4823	2.1	C		C	C
Hypopharynx[c]	3531	960	597	3038	0.7	NC		NC	NC
Larynx	4347	2330	1800	2768	1.9	C		NC	NC
Liver	7165	1039	703	6498	0.9	C		NC	NC
Nasal cavity	562	284	220	360	1.4	C		C	C
Oropharynx[c]	3776	1322	913	2998	0.8	NC		NC	NC
Oesophagus	6047	839	530	5580	0.6	NC		NC	NC
Pancreas	4930	418	345	4607	1.1	C		C	C
Penis[b]	336	231	207	146	1.8	–		–	–
Pleural mesothelioma	592	32	15	579	0.7	NC		NC	NC
Prostate	52279	44567	39590	14736	2.8	C		C	C
Salivary glands[b]	368	220	190	192	2.2	–		–	–
Small intestine	710	359	296	435	1.7	C		C	NC
Urinary tract	722	324	268	472	1.9	C		C	C

C: cure; NC: no cure.
[a] At 15 years or on June 30, 2013.
[b] Not analysed because < 500 cases at diagnosis and < 200 deaths.
[c] Cancer sub-sites.

recorded by FRANCIM (the French network of cancer registries). FRANCIM data are checked for quality and completeness every four years by an independent audit committee (Comité d'Évaluation des Registres).

The considered cancer sites adopted the definitions of the International Classification of Diseases for Oncology, 3rd revision (ICD-O-3) [12]. To ensure sufficient numbers of events to fit the parametric flexible model that uses restricted cubic splines with potentially up to 20 parameters (see Methods section), cancer sites with < 500 cases and < 200 deaths were excluded from the analysis. These were choroid, lip, salivary gland cancers, malignant neoplasm without specification of site as well as penis cancer in men and bone, nasal cavity, pleural mesothelioma and urinary tract cancers in women. These exclusions left 27 sites and 7 subsites for analysis.

As in previous FRANCIM studies [13], age at diagnosis was considered in four groups: < 45, 45–54, 55–64, and 65–74 years. In 11 sites in men and 7 in women, the first two age groups had to be pooled because the number of cases was < 50. Patient vital status was followed over 15 years after diagnosis or up to June 30, 2013. The proportion of deceased patients was 49% and the proportion of patients lost to follow-up was 2.6% (Table 1 in men and Table 2 in women).

2.2. Methods

2.2.1. Estimation of net survival without assumption of cure

For each sex and Département (French administrative area), the expected mortality rates were derived from the general population mortality rates provided by the Institut National de la Statistique et des Études Économiques (INSEE). These rates were "observed" mortality rates (obtained simply by dividing the observed number of death by the corresponding number of person-years). These observed rates presented random (Poissonian) variation and were thus smoothed in order to obtain their expected values. This work was done by the Biostatistical unit of the Hospices Civils de Lyon, using *mgcv* package of R software.

The net survival was estimated using a flexible parametric model on the log cumulative excess hazard scale with restricted cubic spline function of log time [14,15]. In this model, the log cumulative excess hazard is forced to be linear beyond the boundary knots. The splines had four internal knots located at the 25th, 50th, 75th, and 95th percentiles of the observed death times and boundary knots located at the 1st percentile of the observed death times and at 17 years. A separate model was fitted for each cancer site and sex. Age was included in the model as a categorical variable. Its time-dependent effect was added for each category (splines with two internal knots located at the 33rd and 67th percentiles of the observed death times) and evaluated with a

Table 2
Results of checking the assumption of cure by age-group at diagnosis in women.

Cancer site	Number at diagnosis	Number at 5 years	Number at 10 years	Number deaths[a]	Percentage of loss to follow-up[a]	15–44 years	45–54 years	55–64 years	65–74 years
Bones[b]	323	214	197	131	3.1	–	–	–	–
Breast	71947	63289	58145	16125	3.4	C	C	C	C
Central nervous system	2148	510	435	1745	1.9	C	C	NC	NC
Cervix uteri	4407	3126	2918	1586	4.7	C	C	C	C
Choroid[b]	317	240	206	123	1.6	–	–	–	–
Colon[c]	11282	7129	6383	5182	3.8	C	C	C	C
Colon and Rectum	18510	11749	10454	8536	3.7	C	C	C	C
Corpus uteri	7315	5580	5118	2436	3.4	C	C	C	C
Head and neck	2397	1213	968	1503	1.9	C	NC	NC	NC
Kidney	2931	2188	1980	1051	3.8	C	C	C	C
Lip[b]	73	63	60	18	9.6	–	–	–	–
Lung	6785	1492	1223	5647	1.5	C	C	NC	NC
Malignant neoplasm without specification of site[b]	98	28	26	72	6.2	–	–	–	–
Nasopharynx[b,c]	109	67	61	51	4.6	–	–	–	–
Oral cavity[c]	708	413	323	416	2.3	NC	NC	NC	NC
Ovary	5753	2778	2256	3596	2.5	C	C	C	C
Rectum[c]	7228	4620	4071	3354	3.5	C	C	C	C
Skin melanoma	5466	5005	4794	783	6.2	C	C	C	C
Stomach	2264	779	672	1627	4.0	C	C	C	C
Thyroid	6702	6486	6342	448	4.2	C	C	C	C
Tissue sarcoma	849	528	473	397	4.7	C	C	C	C
Tongue[c]	605	310	262	360	2.8	C	NC	NC	NC
Vagina and Vulva	683	411	358	344	4.5	C	C	C	C
						15-54 years		55-64 years	65-74 years
Biliary tract	1084	224	194	899	2.1	C		C	C
Bladder	1233	655	571	707	3.6	C		C	C
Hypopharynx[b,c]	242	85	53	196	2.5	–		–	–
Larynx	419	250	217	224	2.4	C		NC	NC
Liver	1295	223	175	1125	1.8	C		C	C
Nasal cavity	165	82	69-	99	4.2	–		–	–
Oropharynx[b,c]	665	317	252	427	2.6	C		C	C
Oesophagus	862	169	126	745	1.6	NC		NC	NC
Pancreas	3239	357	286	2967	0.9	C		C	C
Pleural mesothelioma[b]	175	20	16	160	2.3	–		–	–
Salivary glands[b]	279	222	210	74	5.7	–		–	–
Small intestine	527	305	255	283	4.2	C		C	C
Urinary tract[b]	254	111	90	169	2.0	–		–	–

C: cure; NC: no cure.
[a] At 15 years or on June 30, 2013.
[b] Not analysed because < 500 cases at diagnosis and < 200 deaths.
[c] Cancer sub-sites.

likelihood ratio test with 0.05 as significance level. Net survival and excess mortality rate curves were drawn for each combination of cancer site, sex, and age group.

2.2.2. Estimation of net survival with assumption of cure

The net survival was estimated using the flexible parametric net survival cure model developed by Andersson et al. [16,17]. This model derives from the net survival model without assumption of cure [14]. The assumption of cure adds the constraint that the log cumulative excess hazard has to be constant (slope = 0) beyond the last boundary knot. The modelling strategy was identical to that without assumption of cure, except an additional internal knot located at the 99th percentile. The latter additional knot allowed an optimal estimation of net survival with the cure model.

2.2.3. Assumption of statistical cure

The assumption of statistical cure was assessed graphically by site, sex, and age group using the excess mortality rate modelled without assumption of cure. The estimated excess mortality rate was considered negligible in case of sustained value ≤ 0.05 and the net survival was modelled with assumption of cure. The adequacy of the estimates of net survival using flexible models with and without assumption of cure was evaluated by checking whether the curves overlap. In case of satisfactory adequacy, cure was considered acceptable and the cure proportion and time-to-cure were estimated.

2.2.4. Indicators of cure from cancer

Two cure indicators were estimated only for combinations of site, sex, and age for which the assumption of cure was accepted:

- The cure proportion (P) commonly provided in statistical cure studies [2–4,10] is the proportion of patients who will never die from the cancer under study. Its value ranges from 0 to 1.
- The time-to-cure was recently defined as TTC by Boussari et al. [5] using P(t), the individual probability for a patient with given characteristics (sex and age at diagnosis) of belonging to the cured group knowing that he/she is still alive at time t [11]:

$$P(t)=\frac{P}{S_n(t)}$$

with $S_n(t)$: the net survival estimated at t

Cure models assume that a given patient belongs to a given group (cured or uncured) since diagnosis. For $t = 0$, $S_n(t)=1$ thus $P(t) = P$. For $t \rightarrow +\infty$, $S_n(t) \rightarrow P$; thus $P(t) \rightarrow 1$. In other words, the probability P(t) that this patient belongs to the cured group is P at the time of diagnosis and increases as time goes by and the patient is still alive. We defined the TTC as TTC_95: i.e., the time t after diagnosis after which P(t) exceeds 95% [5]. The confidence intervals relative to P and TTC were calculated by the Delta method.

stpm2 command in STATA™, release 14 (STATA corp., College Station, Texas) was used to fit flexible parametric net survival models with and without cure option [17,18].

3. Results

Overall, 335 358 solid tumours from 22 cancer sites in men and 21 in women were included. The most frequent were breast (49% of women cancers), prostate (28% of men cancers), lung (16% in men and 5% in women) and colorectal cancer (15% in men and 13% in women).

The assumption of statistical cure for each cancer site, sex, and age-group combination was checked using the excess mortality rate and the net survival curves. The graphs used to check the assumption of statistical cure are presented in Appendix A and the results of the checks in Table 1 for men and Table 2 for women. The assumption of cure was rejected for: cancers of the oesophagus and the oral cavity in both sexes; larynx, lung, and tongue cancers in both sexes and age group 55–74; hypopharynx, pleural mesothelioma, and oropharynx cancers in men; bone, liver, and small intestine cancers in men aged 65–74; head and neck cancers in all men and in women aged 45–74; and central nervous system cancers in men aged 15–44 and men and women aged 55–74.

In cases with accepted assumption of cure, Tables 3 and 4 show, respectively, in men and women, P and TTC values (with their 95% CIs) and the lower left quadrant of Appendix A provides P(t). These results are described below according to three ranges of TTC: < 5 years, 5–10 years, and > 10 years. In Figs. 1–3, adapted from Verdecchia et al.

Table 3
Estimated values of the cure proportion (P) and time-to-cure (TTC) in men by cancer site and age at diagnosis.

Cancer site	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)
	15-44 years		45-54 years		55-64 years		65-74 years	
Bones	47 (39-54)	10.0 (0.6-19.5)	59 (40-73)	10.7 (0.0-22.6)	35 (19-50)	11.8 (0.0-26.0)	NC	NC
Central nervous system	NC	NC	15 (12-18)	10.7 (3.8-17.6)	NC	NC	NC	NC
Colon[a]	59 (55-64)	9.2 (4.3-14.1)	58 (55-60)	9.4 (6.6-12.3)	55 (53-57)	10.0 (8.1-11.9)	48 (46-50)	10.8 (9.3-12.3)
Colon and Rectum	58 (55-61)	9.3 (5.9-12.8)	55 (53-57)	9.9 (8.0-11.7)	53 (51-54)	10.3 (9.0-11.6)	47 (45-48)	10.9 (9.7-12.0)
Kidney	74 (69-79)	8.9 (3.0-14.8)	61 (57-64)	11.7 (9.4-14.0)	58 (55-62)	11.9 (9.9-13.9)	49 (45-53)	12.5 (10.5-14.6)
Lung	13 (11-15)	10.3 (5.2-15.4)	11 (10-12)	10.7 (8.2-13.1)	NC	NC	NC	NC
Nasopharynx[a]	55 (41-67)	11.0 (2.1-19.9)	41 (29-53)	11.8 (2.7-20.8)	32 (21-43)	12.2 (2.2-22.2)	NC	NC
Rectum[a]	57 (52-62)	9.3 (4.3-14.4)	53 (50-56)	10.3 (7.8-12.8)	50 (47-52)	10.6 (8.8-12.5)	45 (42-47)	11.1 (9.4-12.8)
Skin melanoma	84 (81-86)	5.1 (3.9-6.2)	83 (79-86)	5.2 (3.8-6.6)	85 (81-88)	4.9 (3.5-6.2)	79 (75-82)	5.9 (4.2-7.6)
Stomach	29 (24-34)	9.4 (2.2-16.5)	25 (22-28)	9.6 (4.8-14.4)	22 (20-24)	9.8 (6.0-13.6)	19 (17-21)	10.0 (6.7-13.3)
Testis	96 (95-97)	0	96 (92-98)	0	81 (71-88)	2.6 (0.0-7.2)	90 (72-96)	1.3 (0.0-3.4)
Thyroid	98 (95-99)	0	91 (87-94)	1.7 (0.1-3.3)	81 (74-86)	7.7 (4.7-10.6)	63 (53-72)	9.7 (5.3-14.1)
Tissue sarcoma	56 (50-62)	7.6 (2.9-12.4)	58 (49-66)	8.8 (2.7-14.9)	45 (38-53)	8.8 (1.8-15.8)	48 (39-56)	7.3 (0.4-14.2)
Tongue[a]	37 (30-44)	11.8 (6.5-17.1)	NC	NC	NC	NC	NC	NC
	15-54 years				55-64 years		65-74 years	
Biliary tracts	22 (16-30)	9.1 (0.0-22.4)			15 (11-21)	10.5 (0.1-20.9)	16 (13-20)	9.8 (1.0-18.6)
Bladder	56 (52-59)	11.6 (9.3-13.9)			49 (46-51)	12.0 (10.3-13.7)	37 (34-39)	12.6 (11.0-14.2)
Larynx	37 (34-40)	13.1 (11.1-15.1)			NC	NC	NC	NC
Liver	15 (12-17)	10.0 (4.5-15.4)			NC	NC	NC	NC
Nasal cavity	42 (33-51)	12.0 (6.5-17.4)			33 (24-41)	12.4 (6.1-18.7)	33 (25-41)	12.3 (6.2-18.5)
Pancreas	10 (8-12)	7.9 (0.0-15.8)			5 (4-7)	8.8 (0.7-16.9)	6 (4-7)	8.2 (0.8-15.6)
Prostate	82 (78-85)	11.5 (9.6-13.3)			88 (86-89)	10.0 (9.0-11.0)	80 (78-82)	12.3 (11.7-12.9)
Small intestine	50 (40-58)	11.3 (5.0-17.6)			42 (33-51)	11.6 (4.9-18.3)	NC	NC
Urinary tracts	48 (37-58)	8.1 (0.0-18.9)			43 (35-50)	8.5 (0.2-16.9)	36 (30-43)	9.0 (1.2-16.7)

NC: No Cure.
[a] Cancer subsite.

Table 4
Estimated values of the cure proportion (P) and time-to-cure (TTC) in women by cancer site and age at diagnosis.

Cancer site	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)	P (95% CI)	TTC (95% CI)
	15-44 years		45-54 years		55-64 years		65-74 years	
Breast	72 (71-74)	12.1 (11.5-12.7)	80 (80-81)	10.6 (10.0-11.1)	79 (78-79)	11.2 (10.6-11.8)	73 (71-74)	12.3 (11.7-12.9)
Central nervous system	38 (33-42)	10.4 (6.2-14.5)	19 (15-23)	10.8 (3.3-18.3)	NC	NC	NC	NC
Cervix uteri	77 (75-79)	6.5 (4.3-8.7)	63 (60-67)	8.5 (4.6-12.5)	49 (45-53)	11.0 (7.6-14.5)	46 (42-51)	10.7 (6.3-15.2)
Colon[a]	62 (58-66)	7.4 (3.8-11.1)	62 (59-64)	6.8 (4.5-9.2)	58 (56-60)	8.1 (6.1-10.1)	55 (53-57)	8.6 (6.9-10.2)
Colon and Rectum	62 (59-65)	7.6 (4.8-10.4)	59 (57-61)	8.1 (6.2-10.0)	58 (57-60)	8.5 (7.1-10.0)	53 (52-55)	9.2 (7.9-10.5)
Corpus uteri	81 (75-86)	6.8 (0.3-13.3)	77 (73-79)	8.4 (5.0-11.8)	75 (73-77)	8.8 (6.5-11.1)	63 (60-65)	10.9 (8.8-13.0)
Head and Neck	40 (33-47)	12.3 (8.2-16.4)	NC	NC	NC	NC	NC	NC
Kidney	79 (73-84)	7.9 (1.1-14.6)	73 (68-78)	9.7 (5.0-14.5)	68 (63-72)	11.4 (8.7-14.1)	54 (49-58)	12.2 (9.7-14.7)
Lung	23 (20-27)	9.6 (4.0-15.2)	16 (14-18)	10.6 (6.7-14.5)	NC	NC	NC	NC
Ovary	62 (58-66)	8.4 (5.5-11.4)	43 (39-46)	10.3 (7.6-12.9)	32 (30-35)	10.4 (7.7-13.2)	22 (20-25)	11.1 (7.9-14.3)
Rectum[a]	62 (56-67)	8.5 (3.8-13.2)	57 (53-60)	9.3 (6.4-12.2)	59 (56-61)	9.1 (6.8-11.4)	50 (48-53)	10.1 (7.9-12.3)
Skin melanoma	92 (90-93)	3.8 (3.0-4.6)	90 (87-92)	5.1 (3.6-6.5)	87 (83-89)	6.4 (4.4-8.5)	80 (75-84)	8.8 (5.2-12.5)
Stomach	31 (25-38)	9.1 (0.0-18.9)	32 (26-37)	8.9 (0.7-17.2)	32 (27-36)	9.6 (3.7-15.5)	25 (22-28)	10.1 (5.5-14.7)
Thyroid	99 (98-100)	0	99 (97-100)	0	97 (94-98)	0	83 (76-89)	9.9 (7.5-12.3)
Tissue sarcoma	65 (58-71)	9.3 (3.0-15.6)	63 (54-71)	9.5 (1.9-17.1)	42 (34-49)	11.3 (4.3-18.2)	35 (27-42)	11.6 (4.6-18.7)
Tongue[a]	44 (31-56)	12.0 (4.5-19.5)	NC	NC	NC	NC	NC	NC
Vagina and Vulva	70 (57-80)	10.7 (3.4-17.9)	61 (50-71)	11.4 (5.5-17.4)	43 (34-52)	12.4 (7.0-17.7)	38 (31-45)	12.4 (8.2-16.6)
	15-54 years				55-64 years		65-74 years	
Biliary tracts	28 (21-35)	7.2 (0.0-17.0)			20 (16-25)	7.6 (0.0-16.6)	13 (11-16)	8.1 (0.4-15.9)
Bladder	46 (39-54)	11.8 (6.1-17.5)			44 (38-51)	11.9 (7.0-16.8)	40 (35-45)	12.1 (8.4-15.8)
Larynx	52 (41-61)	13.0 (8.4-17.7)			NC	NC	NC	NC
Liver	22 (17-27)	8.9 (0.8-17.1)			14 (10-17)	9.5 (0.4-18.5)	6 (4-7)	10.1 (0.3-20.0)
Oropharynx[a]	27 (21-32)	12.1 (6.6-17.5)			31 (24-39)	11.9 (5.7-18.0)	25 (17-34)	12.1 (3.5-20.7)
Pancreas	16 (13-19)	8.4 (1.6-15.2)			9 (7-11)	9.0 (2.0-15.9)	4 (3-5)	9.5 (2.3-16.7)
Small intestine	52 (42-61)	11.2 (5.6-16.7)			46 (36-55)	11.4 (5.4-17.5)	29 (21-37)	12.1 (5.3-18.9)

NC: No Cure.
[a] Cancer subsite.

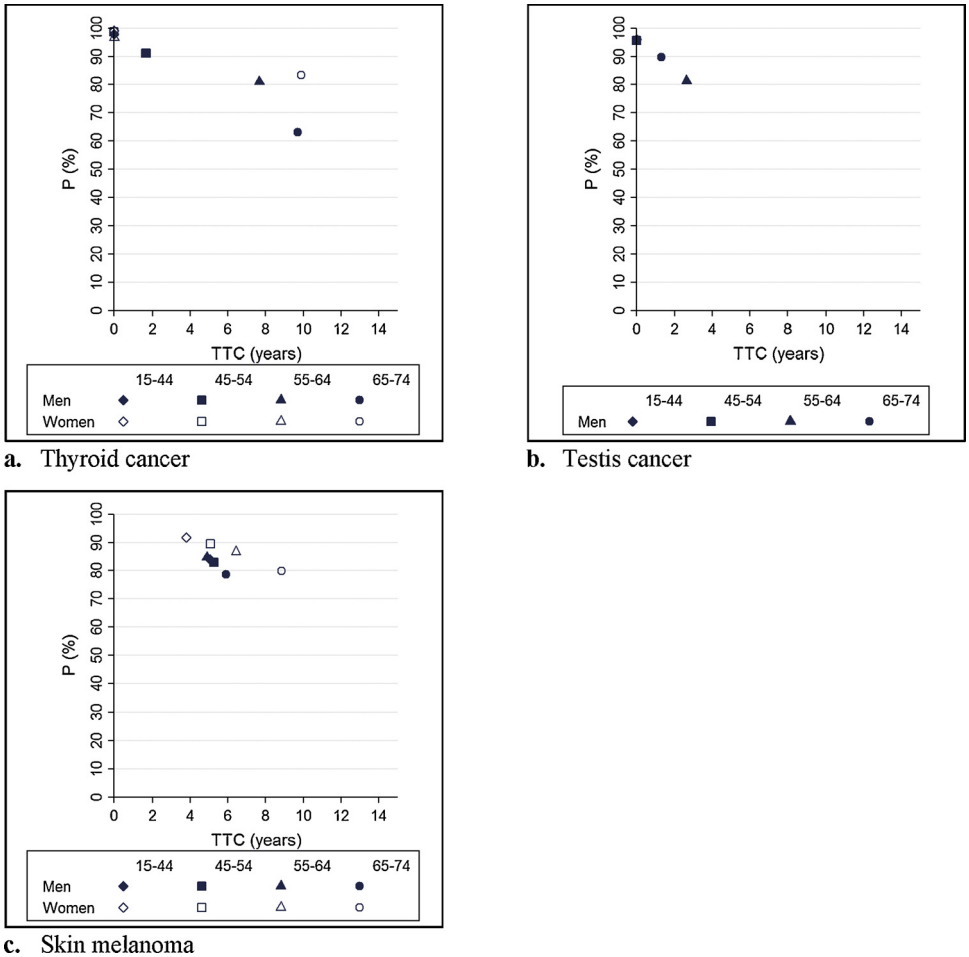

Fig. 1. Cure proportion (P) and time-to-cure (TTC) in cancer sites with TTC ≤ 5 years for some combinations of sex and age at diagnosis. a) Thyroïd cancer, b) Testis cancer and c) Skin melanoma.

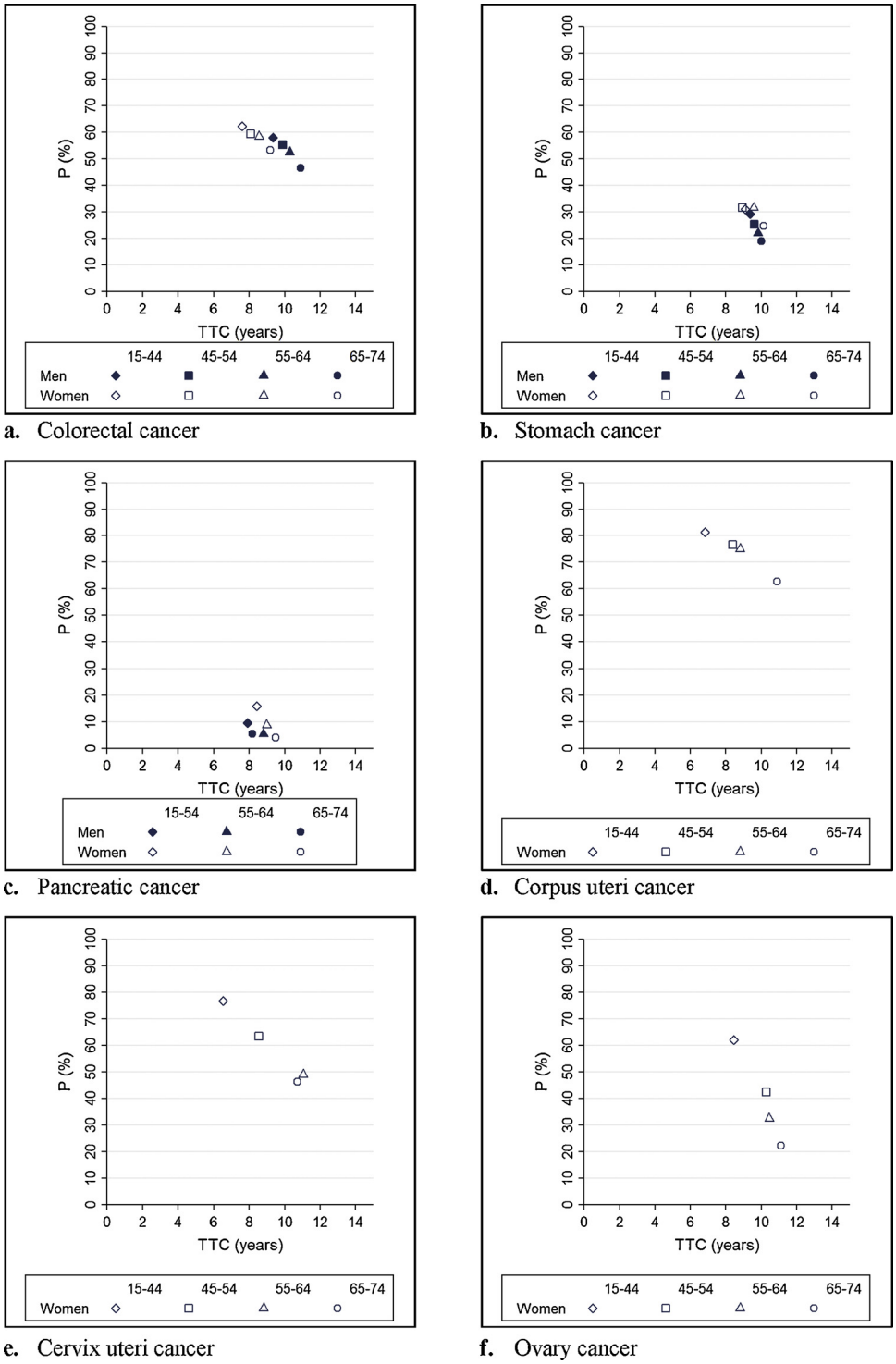

Fig. 2. Cure proportion (P) and time-to-cure (TTC). Examples of cancer sites with TTC between 5 and 10 years for some combinations of sex and age at diagnosis. a) Colorectal cancer, b) Stomach cancer, c) Pancreatic cancer, d) Corpus uteri cancer, e) Cervix uteri cancer and f) Ovary cancer.

[10], P is plotted against TTC to show changes of P and TTC values with sex and age and allow visual comparisons between cancer sites.

3.1. *Time-to-cure < 5 years (Fig. 1)*

Thyroid and testis cancers and skin melanoma had the shortest TTC. Cure was considered reached right after diagnosis (P > 95% thus TTC = 0) in thyroid cancer in men and women aged 15–44 and in women aged < 65 (Fig. 1a) and in testis cancer in men aged < 55 (Fig. 1b). TTC was < 2 years and P was > 80% in men aged 45–54 with thyroid cancer and men aged ≥55 with testis cancer. Cure from skin melanoma was reached within 5 years (Fig. 1c) in all patients aged < 55 and in men aged 55–64; P was around 90% in women and 85% in men. Though P was > 60%, cure was reached after 6–10 years in all patients aged 65–74 and men aged 55–64 with thyroid cancer and in all patients aged 65–74 and women aged 55–64 with skin melanoma.

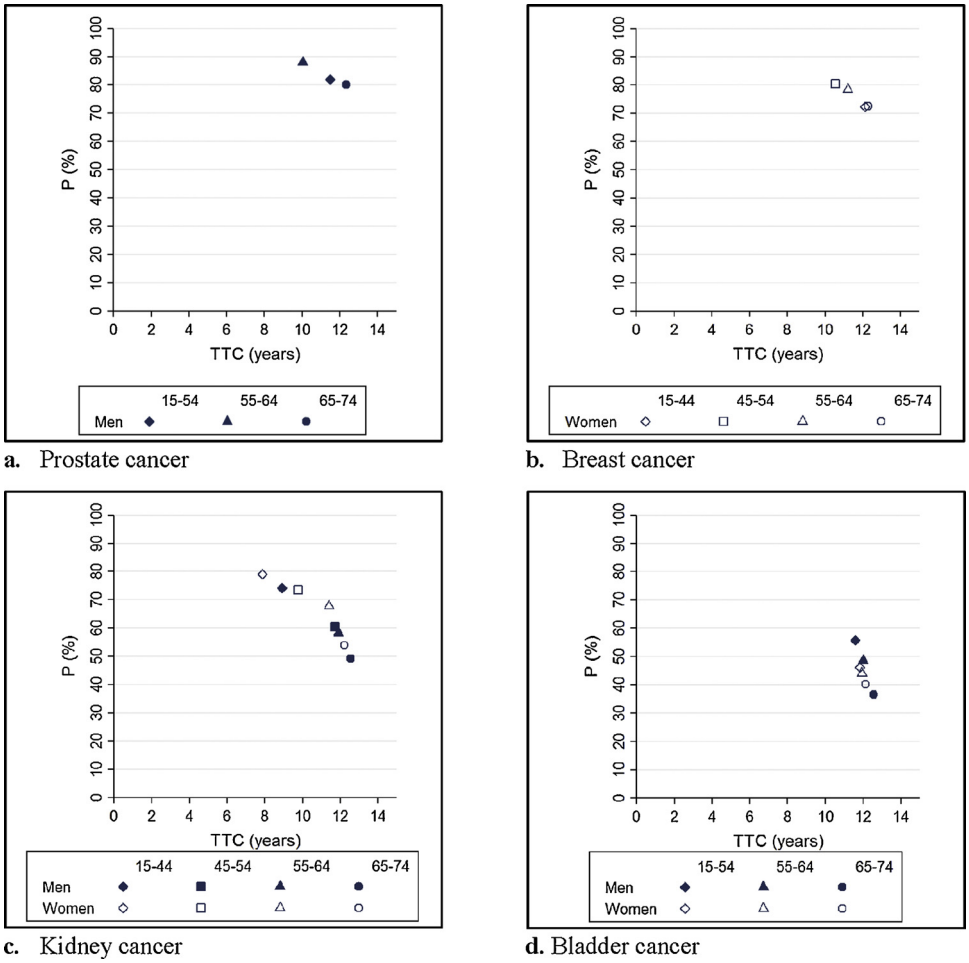

Fig. 3. Cure proportion (P) and time-to-cure (TTC). Examples of cancer sites with TTC > 10 years for most combinations of sex and age at diagnosis. a) Prostate cancer, b) Breast cancer, c) Kidney cancer and d) Bladder cancer.

3.2. Time-to-cure 5–10 years (Fig. 2)

In all digestive cancers (except small intestine) and all gynaecologic cancers (except breast), cure was reached within 5–10 years.

Among digestive cancers, P was the highest in colorectal cancer (Fig. 2a). P was slightly higher in women vs. men and decreased with age from 62 to 55% in women and from 59 to 48% in men. The TTC increased with age and cure was reached earlier in women vs. men. The TTC ranged from 6.8 to 9.2 years in women and from 9.3 to 10.8 years in men. P was the lowest in pancreas cancer (Fig. 2c). Under 45 years, P was 10% in men and 16% in women and about 5% in older patients. The TTC ranged from 8 to 9 years and did not change with sex or age. For stomach cancer (Fig. 2b), P decreased with age from 30 to 19% in men and from 30 to 25% in women. The TTC ranged from 9 to 10 years whatever the sex and age.

Among gynaecologic cancers, P was overall higher for corpus uteri than for cervix uteri or ovary (Fig. 2d). It decreased with increasing age from 81 to 63%. The corresponding figures for cervix uteri were 77% and 46% (Fig. 2e). For corpus and cervix uteri, the TTC was similar and increased with age from 7 to 11 years. For ovary, P decreased with increasing age from 62 to 22% (Fig. 2f). Cure was reached at 8.4 years in the youngest and 11 years in the oldest.

3.3. Time-to-cure > 10 years (Fig. 3)

Cure was reached past 10 years in urinary tract (kidney and bladder), breast and prostate cancers. For prostate and breast cancers (Fig. 3a and b), TTC ranged between 10 and 12 years though P was very high. P varied with age between 80 and 88% for prostate cancer and between 72 and 80% for breast cancer.

P was higher for kidney than for bladder cancer (Fig. 3c and d). For kidney, P decreased with increasing age from 74 to 49% in men and from 79 to 54% in women. For bladder, P ranged from 56 to 37% in men and from 46 to 40% in women. For kidney cancers diagnosed after age 45, the TTC ranged from 12 to 13 years in men and from 10 to 12 years in women. For bladder, cure was reached within 12–13 years whatever the sex and age.

4. Discussion

Among the 335,358 cancer cases registered 1989–2009 in patients aged 15–74 years, the TTC was < 12 years for most cancer sites.

With cure proportions > 95%, cure occurred right after diagnosis in men aged < 55 with testis cancer and in men < 45 and women < 65 with thyroid cancer. For skin melanoma, testis cancers and thyroid cancers diagnosed before age 65, the cure proportions were > 80% and cure was reached within 5 years. For breast and prostate cancers (the most frequent in France), cure occurred after 10 years despite very high cure proportions (72–88%). For colorectal cancer, cure was reached between 5 and 10 years.

Previous studies have reported net survival advantages in women vs. men [19]. Here, we show higher cure proportions in women than in men in nearly all cancer sites, except tissue sarcoma, biliary tract, and bladder cancers. Regarding TTC, sex disparity was not uniform; e.g., the TTC was shorter in women regarding colorectal or kidney cancer but longer regarding skin melanoma or tissue sarcoma. In both sexes and

most cancer sites, the TTC increased and the cure proportion decreased with increasing age at diagnosis. Plotting TTC vs. P depicts the proportion of patients to whom the TTC applies. For instance, when P is very low (melanoma or cancer of the lung or the pancreas), the TTC has less importance than when P is very high.

Regarding age disparities, the rejection of the cure assumption in the older age groups in several cancer sites was in agreement with net survival studies on the same French registry data [13] (absence of plateau in the corresponding sites/age groups).

To be excluded, a cancer site had to meet both conditions of < 500 incident cases and < 200 deaths. This allowed keeping in the analysis cancers with good prognosis and reasonable numbers of incident cases. Among the cancer sites excluded because the number of cases was < 500 and the number of deaths was < 200, only penile cancer had a low excess mortality rate. However, in France, penile cancer is rare: its crude incidence rate is 1.14 per 100,000 person-years [20].

This study is the first to provide cure proportions and TTC for cancers in France. Its strengths are: i) the exhaustiveness of the study due to a population-based recruitment; ii) the use of flexible parametric cure models that have shown advantages over other approaches [21]; iii) almost exact overlap of model-estimated net survivals with and without cure when the assumption of cure was accepted; and iv) the use of a recent definition of TTC [5]. Indeed, for the first time, the TTC was estimated from the individual probability of being cured [5]. This intuitive definition of TTC indicates the time after which patients can be reasonably confident in belonging to the cured group. From this time, the observed mortality rate equals the mortality of the general population. Although statistically cured patients would not die from cancer, they are still subject to death from other causes with the same probability as the general population.

Only two previous studies have estimated the time-to-cure from the net survival of the uncured [22] and from the 10-year conditional net survival (survival for additional 10 years) [4], but with limitations [5]: the former can be over-influenced by the early excess mortality because it depends only on the survival of the uncured. For a given long-term excess mortality, a high early excess mortality brings the estimate of this time-to-cure closer to the date of diagnosis than a lower early excess mortality. The latter assumes a monotonously increasing function for the conditional net survival and requires long-term follow-ups. Only one study has been published with estimations of the time-to-cure [4] using the conditional net survival. Our results are similar to those obtained by Dal Maso et al. [4], particularly regarding sex-related and age-related differences. However, there are two discrepancies i) when P > 95%, TTC values here are 0 vs. 1–2 year in men < 55 years with testicular cancer and 1–4 years in women < 65 years with thyroid cancer in the Italian study; ii) TTC of 10 years here vs. 5 years in women aged 65–75 with thyroid cancer in the Italian study (probably because of lack of monotony: in our data, the 10-year conditional net survival decreased between 5 and 8 years then increased to reach 95% only 10 years after diagnosis). The similarity of the results between our study and the Italian study are in agreement with the 5-year survivals found in EUROCARE studies [23]. Applied to other countries with different health policies (e.g., cancer prevention or screening) or with different risk factors due to different lifestyles, this method might show different TTCs for same cancer sites.

One limitation of the present study is the lack of information on well-recognised prognostic factors such as cancer stage. The main limitation of all cure models is the absence of implemented statistical tests. This imposes a graphical checking of the assumption of cure that requires criteria. Our criteria (excess mortality ≤0.05 and adequacy of net survival curves) may be questioned: different criteria would have led to different selections of cancer site, sex, and age combinations; furthermore, the threshold used to define TTC was arbitrarily chosen. Moreover, the post estimation of the TTC might have yielded very wide confidence intervals in case of low cancer incidence or lethal cancer. We are currently developing a cure model that includes time-to-cure (defined as the time at which the excess mortality rate becomes null) as a parameter to estimate. This approach will allow testing the assumption of cure and will provide a more accurate estimation of the time at which cure is reached because it will not use an approximation based on a predefined threshold.

Although statistical cure is not directly related to clinical cure, the cure proportion and the TTC are important indicators for policy making, medical practice, and patient information. In France, cancer patients cannot access to credit or have to pay high extra insurance premiums; however, since 2015, cancer declaration is no more mandatory ≥10 years after the end of cancer treatment (also called: “right to be forgotten”) [24]. The present results suggest that the durations of extra premiums should be shortened, not only after testis cancer, thyroid cancer, and skin melanoma where statistical cure occurs shortly after diagnosis, but and also after other cancers whose cure is reached ≤10 years after diagnosis.

Authorship contribution

- Substantial contributions to conception and design: GR, OB, NB, LR, MC, VJ.
- Acquisition of data: MC, VJ.
- Analysis and interpretation of data: GR, OB, VJ.
- Drafting the article or revising it critically for important intellectual content: all authors.
- Final approval of the version to be published: all authors.

Funding

This work was supported by the Institut National du Cancer, France [grant INCa 2014-087].

Declarations of interest

None.

Acknowledgements

The authors wish to thank the French network of cancer registries (FRANCIM) for providing the study data. They also thank Stéphanie Normand (Registre Bourguignon des Cancers Digestifs, France) for her technical assistance.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.canep.2019.02.006.

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