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What is the most appropriate period to define synchronous cancers?

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Abstract

Background

Studies about second primary cancers (SPC) incidence exclude a period following the first cancer diagnosis given the high probability of diagnosing another primary cancer during this phase (synchronous cancers). However, definition of synchronicity period varies widely, from one to six months, without clear epidemiological justification. The objective of this study was to determine the most appropriate synchronicity period.

Methods

Data from 13 French population-based cancer registries were used to establish a cohort of all patients diagnosed with a first cancer between 1989 and 2010. The incidence rate of subsequent cancer was computed by day within 1 year of follow-up after the first diagnosis. Incidence was modelized by joinpoint regression models with an initial quadratic trend and a second constant part (plateau). The joinpoint was the point from which the plateau began and defining the synchronicity period.

Results

Our cohort included 696,775 patients with a first cancer, of which 12,623 presented a SPC. The median joinpoint for all sites combined was estimated at 120.5 days [112.0-129.0]. Analysis by gender reported a higher difference in 32 days for males (127.8 vs 96.1 days). Noteworthy differences were found depending on patient age and the site of first cancer, with joinpoint ranging from 84.7 (oesophagus cancer) to 250.1 days (bladder cancer).

Conclusion

Although some heterogeneity was observed based on the characteristic of the patients, the appropriate synchronicity period appears to be 4 months after the diagnosis of first cancer.

Keywords (Mesh): synchronous cancer, second primary, neoplasms, registries

Word count: 2999

Abbreviations:

CI, confidence interval; IARC, International Agency for Research on Cancer; PYR, person-year at risk; SIR, standardized incidence ratio; SD, standard deviation; SPC, second primary cancer.

Introduction

As early detection and treatment of cancer improves, survival of cancer patients generally increases as well as the probability of diagnosing a second primary cancer (SPC) (1). Data from cancer registries are commonly used to study the incidence of SPCs at a population-based level (2–4). The person-year approach is frequently used in these studies which allows to estimate a standardized incidence ratio (SIR). The SIR is calculated as the ratio between the observed number of second cancers and the number expected in the reference population. The SIR can be interpreted as the "relative risk" of SPC among cancers survivors compared with the risk of cancer in the general population. In France, *Gass et al*. used the data from the FRANCIM Network to estimate an overall SIR of 1.29 (5), corresponding to an increase in the risk of second cancer by 29% compared with the general population. To evaluate the risk of SPCs at the best, objective studies about SPC incidence generally exclude a period following the date of the first cancer diagnosis (synchronicity period)(6). Indeed, at the time of cancer diagnosis, many examinations are performed to precise the cancer's nature and extension. This high diagnostic pressure may lead to the detection of other not yet symptomatic cancers, thus leading to a certain overdiagnosis. In addition, the lack of comparable population subjected to the same diagnostic pressure leads to a biased estimate of the SIR in this time of synchronicity period. Studies on SPCs therefore only include metachronous cancers. In most studies, a time interval of 2 months is considered to define the synchronicity period, especially in France (2,5), USA (SEER program) (7–9), and in many European countries (10–12). However, some authors chose a period of 1 month (13–15), 3 months (3,16), 4 months (17) or 6 months (18,19) without any clear epidemiological justification.

The objective of this study was thus to determine the most appropriate time interval to define the synchronicity period.

Methods

Data source and management

Data from 13 French population-based cancer registries from the FRANCIM Network and participating in the K2-France study were used to establish a population-based cohort. This cohort included all patients presenting with a first cancer diagnosed between 1989 and 2010, excluding non-melanoma skin cancers. This database was used to study the trends in incidence of SPCs in France with a case-mix approach (5) and is an update of a previous cohort describing the cases diagnosed between 1989 and 2004 (2). The data come from

registries covering 12 administrative regions of France (Bas-Rhin, Calvados, Doubs, Haut-Rhin, Hérault, Isère, Lille area, Loire-Atlantique, Manche, Somme, Tarn and Vendée). These registries are regularly included in the "Cancer Incidence in Five Continents" monograph series (20–22), showing a high degree of completeness of ascertainment. Vital status of all patients was updated by June 30, 2013. The proportion of patients lost to follow-up (i.e. alive at some date before June 30, 2013 and with no SPC) was 2.3%.

SPC was defined as the first subsequent primary cancer occurring after first cancer diagnosis. Extensions, recurrences, or metastases were not considered as a SPC according to the International Agency for Research on Cancer rules (IARC) for multiple primary cancers (23). For the present analysis, computation of person-days at risk began on the day after diagnosis of the first cancer and ended at the date of SPC diagnosis, death or after 365 days of follow-up, whichever came first. Patients diagnosed with simultaneous cancer (<1 day of follow-up) were excluded from the analysis. Third and subsequent primary cancers were not considered as SPCs.

The third edition of the International Classification of Diseases for Oncology was used to code invasive tumors (24). Cancer sites (e.g. head and neck) were defined in accordance with the topography and morphology codes used in the EUROCARE study (25).

Statistical analysis strategy

The steps of the statistical analysis strategy are presented on the figure 1.

We calculated, day after day, the instantaneous incidence rate of SPC within one year of follow-up after the first cancer diagnosis by dividing the daily number of SPC by the number of persons remaining at risk the same day. Subjects deceased or diagnosed with a SPC before the day considered in the computation were excluded from the number of persons at risk.

Incidence rates were modelized using a joinpoint regression model composed of a segmented regression model with an initial quadratic trend and a second constant part (plateau) (26). The joinpoint was the point from which the plateau began and defining the synchronicity period. Univariate estimates of the jointpoint and the plateau were first performed for all patients, then by gender, age, calendar period of first cancer diagnosis and site of first cancer. Analyses by site of first cancer were performed when the number of SPCs exceeded 300 during the first year of follow-up. These analyses were therefore performed for the following sites of first cancer: head and neck, colon, rectum, larynx, lung bronchus and trachea, breast, prostate, bladder, kidney, and non-Hodgkin's lymphoma.

The second stage of the analysis was to assess the change in the SIRs occurring when different synchronicity period were considered: the usual 2-month interval and the result of

the joinpoint regression analysis. The number of observed SPC was compared with the number of expected SPC using the person-years at risk (PYR) approach. The number of expected cancers was calculated by multiplying the PYRs allocated by sex, attained age, year of follow-up and administrative region by the corresponding first cancer incidence rate estimated from the general population. The standardized incidence ratios were obtained by dividing the number of observed SPCs by the expected number. SIRs were computed for the whole cohort, by sex, age, calendar period of first cancer diagnosis and site of first cancer. The relative difference in SIRs according to the length of the synchronicity period (as estimated by the joinpoint regression vs 2 months) was finally computed.

Third, we studied the associations between sites with respect to the occurrence of synchronous primary cancers. Synchronous cancers were defined based on the synchronicity period found in the previous step of the analyses. Analyses were performed for all sites combined and by site of first cancer. Synchronous cancer sites were selected when the proportion exceeded 0.1% among patients with first cancer.

Finally, we performed a sensitivity analysis by modifying two parameters of the model: length of follow-up (from 1 year to 5 years) and the time unit (by week vs day) used to compute the incidence rate. This analysis was performed in order to ensure that the estimation of the joinpoint was not significantly influenced by the length of follow-up after a minimal follow-up of 1 year, neither by the time scale.
All analyses were performed with the SAS statistical software, version 9.3 (SAS Institute, Cary, NC). The same analyses were also performed with the joinpoint Regression Program, Version 4.7.0.0 provided by the National Cancer Institute. This program uses permutation tests to identify changes in trends (27).

Results

Participation

Our cohort included 696,775 patients with a first cancer diagnosed between 1989 and 2010 within the area covered by participant registries. We excluded 9,968 (1.4%) patients censored at the first day (death or second primary). In the remaining cohort of 686,807 patients, 56.4% were males. The mean age at diagnosis of the first cancer was 65.2 years (SD 14.8). During the first year of follow-up, 12,623 (1.8%) patients presented an SPC and 164,328 (23.9%) died before developing an SPC.

Univariate analyses

After an initial decay, the instantaneous incidence rate reached a constant risk of SPC at 3.9/100,000 person-days at risk. Figure 1 shows the incidence of SPC modelled with joinpoint regression. For all sites combined, the joinpoint was estimated at 120.5 days (95% CI= [112.0-129.0]).

Univariate analyses are presented in table 1. Analyses by gender showed a gender-effect with a difference of about 30 days between males and females (127.8 in males vs 96.1 days in females). Furthermore, we observed an increase in the value of the joinpoint with age, up to 75 years-old patients (98.3 days for patients younger than 44 years old vs 137.4 days for patients aged 65 to 74 years old). Except for the 1995-1999 calendar period, we also observed an increase in the joinpoint between 1989 and 2010 (105.3 days between 1989 and 1994, 142.2 between 2005 and 2010).

With respect to the analyses by site of first cancer, all joinpoints ranged between 84.7 and 118.3 days, except for prostate and bladder cancers (203.2 and 250.1 days respectively).

Concerning the plateau, the incidence rate of SPC was estimated at 3.9/100,000 person-days (95% CI= [3.7-4.1]). As for the former analysis, we found a difference between gender (5.4/100,000 person-days for males vs 2.3 for females). The incidence for the plateau phase increased with age at first diagnosis (1.0/100,000 person-days for younger patients vs 5.2/100,000 person-days for patients over 75 years). Furthermore, analyses by cancer site showed important differences between sites ranging from 1.6/100,000 person-days after a first breast cancer to 9.7/100,000 person-days after a first head and neck cancer. The calendar period of diagnosis of the first cancer did not influence the value of the plateau (table 1).

Sensitivity analysis

In a sensitivity analysis, the incidence rate was calculated by day and by week. The joinpoint estimated was the same in both computations. Analysis by week was repeated with the Joinpoint Regression Program and showed similar results for the value of the joinpoint (at week 17) and for the plateau (27.2/100,000 person-weeks). We reproduced the model with several intervals of follow-up ranging from 1 to 5 years without significant changes in the value of the joinpoint (from 120.7 to 123.9 days) or for the plateau (from 3.8 to 3.9/100,000 person-days).

Impact on the SIR of the use of different definition of synchronicity period.

Results of the analyses are reported in table 2. During the first year of follow-up, for a usual definition of 2 months, we observed 7,388 SPCs while 5,152.9 were expected, leading to an SIR of 1.43 (95% CI= [1.40-1.47]). With a definition of synchronicity period of 4 months, the SIR was 1.30 (95% CI= [1.27-1.34]).

The relative difference between these two SIRs was -9.1%. In males, we found a greater difference (1.49 vs 1.34; -10.1%). Difference in females was -6.9%. SIR difference was minimal in younger patients (2.99 vs 2.97) while it was -11.0% in patients aged 65 to 74 (1.36 vs 1.21). We also evidenced a calendar period effect, with an increase in the difference for the most recent periods. Indeed, the difference was -3.4% between 1989 and 1994, and reached -12.5% between 2005 and 2010.
Concerning the analyses by site of first cancer, the most important differences were observed for bladder (-26.0%), rectum (-19.7%), prostate (-12.1%), oesophagus (-8.6%) and breast (-7.8%) cancers. However, for rectum, oesophagus and breast cancers, these differences were not statistically significant.

Synchronous cancer site association

Using a 4-months period to define synchronicity period, we found in our cohort that 7,361 patients (1.07%) presented a synchronous cancer. The most common cancer sites detected was the prostate cancer (15.75%), lung, bronchus, and trachea cancers (14.3%) and kidney cancers (8.54%). The colon and the rectum cancers represented 7.74% and 4.68% of second cancers detected. Strong disparities were observed by site of first cancer. The proportion of patients with a synchronous cancer was 4.13% after a first bladder cancer, 3.09% after an oesophagus cancer, 3.00% after a head and neck cancer and 2.35% after a larynx cancer. On the contrary, some other sites showed a very low proportion of patients with a synchronous cancer detected. For instance, only 0.34% of breast cancer patients had a synchronous cancer detected. These results are presented in table 3.

Discussion

Very few studies have been performed on this topic. The Italian AIRTUM Working Group already showed a greater risk of being diagnosed with a SPC during the first months after the diagnosis of the first cancer (6). Our study is the first study attempting to find the most appropriate time interval to define the synchronicity period on an epidemiological basis.

This problem is well-known to population-based studies about the risk of SPCs. These studies used the SIR to estimate the risk of SPC compared to the general population. Many

biases are introduced during the first period following the date of the diagnosis of the first cancer, which is generally excluded from the analyses. Indeed, this period is used by clinicians to define the cancer's nature and extension, by performing many medical exams. The diagnostic pressure undergoes by cancer patients during this period may lead to the detection of other cancers, especially those already present but not symptomatic. Studies about melanoma skins and thyroid cancers showed that the number of cancers detected increased with the number of exams performed (28,29). Autopsy studies also found cancers non-suspected during the patient life (30). The SIR is the ratio between the observed cases in the population of interest and the expected cases in reference population. To estimate the SIR at the best, a reference population of non-cancer patients subjected to the same frequency of medical exams as cancer patients would to be needed. Unfortunately, this population does not exist, and this is the reason why the synchronicity period is excluded in studies on SPCs incidence.

To estimate the effect of excluding cancers detected during the synchronous period, it is important to understand which type of cancer it is. Synchronous cancers detected during intense investigating activity are generally asymptomatic and can be classified into two groups: the indolent cases and the anticipated cases (6). Their exclusion leads to different effects on the estimation of the incidence of second cancers. The indolent cases are cancers would never have been symptomatic in the lifetime of the patients, phenomenon well known in screening programmes or autopsy studies and defined as "overdiagnosis". Their exclusion during the synchronous period should not influence SIR estimates and including them would result in an overestimation. So, their exclusion leads a better estimation of the real risk of SPCs. The anticipated cases are cancers not yet symptomatic which would nevertheless appear few weeks or months later. Their exclusion during the synchronous phase led to an underestimation of the real risk of SPCs in the population of cancer patients. So, to obtain an unbiased estimate of the incidence of SPCs, indolent cancers should be excluded and anticipate cases should be included. Unfortunately, it is impossible to make difference between cases defined as overdiagnosis and diagnosed early.

The length of follow-up is the other mainly parameter who will influence the estimation of the SIR. Indeed, with a period of 2 months to define the synchronous period and a follow-up of 2 months, the observed cases of metachronous cancers will be zero. On the other hand, with a follow-up of several years, the influence of the length of the synchronicity period will be less or even negligible on the estimate of the SIR. For studies with short follow-up, the estimation of the best period of synchronicity is primordial. Thus, with our primary results founding a synchronous period at 4 months instead of 2 months commonly use, SIR for the first year of follow-up has been changed by 9.1%. Analyses by population characteristics and by sites

showed that the relative difference in SIRs were larger in males and increased with age at first cancer and calendar period. The relative difference was higher for sites of first cancer showing a high value of the joinpoint (prostate, bladder, rectum). For other types of objectives, the synchronicity period may be different and its influence should be studied on a case-by-case basis.

To eliminate biases due to the SIR estimation and in particular the absence of a reference population comparable to the cancer patients, we chose to modelized the number of second cancer cases using the incidence by day. We hypothesized that the incidence of second cancers would be higher during the period of high diagnostic pressure and we defined SPCs detected during this phase as synchronous cancers. Preliminary graphic analyses on the data showed a decreasing curve then a constant phase. We applied a joinpoint regression model to identify the point of inflection. Analysis by population characteristics showed some heterogeneity in joinpoint results. Indeed, we observed an increase in the value of the joinpoint with age at first cancer diagnosis and with calendar period. The joinpoint was reached later in males than in females. This result reflects the difference in the distribution of cancer sites according to gender. For instance, prostate and bladder cancers (joinpoint at day 201.2 and 250.6 respectively) represent the two most frequent sites with a high risk of SPC (27.9% of all SPCs). Moreover, the number of SPCs after a prostate or a bladder cancer increased significantly between the first and the last calendar period (number of SPC multiplied by 5.5 for prostate and 4.5 for bladder) explaining the upward trend of global joinpoint.

Bladder, oesophagus, head and neck and larynx cancers were most often associated with synchronous cancers (>2.3% of cases). These sites were associated with each other and with the lung, bronchus and trachea cancers. These associations of synchronous cancers are mainly explained by the common exposure to tobacco or alcohol (31). A SPC in the prostate was significantly associated with kidney and bladder cancers. Several studies also found this association and suggested several explanations. Indeed, some prostate cancers are discovered during the pathological analysis of cystoprostatectomy performed for the treatment of bladder cancer (detection bias). Common risk factors such as high age and smoking, or common pathways in carcinogenesis may also be part of the explanation of this association (32,33).

Conclusion

Although some heterogeneity was observed based on the characteristics of the patients, the most appropriate period to define synchronicity period for study of risk of second primary cancers appears to be 4 months after the diagnosis of a first cancer. Thus, we suggest to

consider this synchronicity period to eliminate some detection biases in the estimation of the risk of metachronous SPC in epidemiological population-based studies.

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Conflicts of interest: none declared

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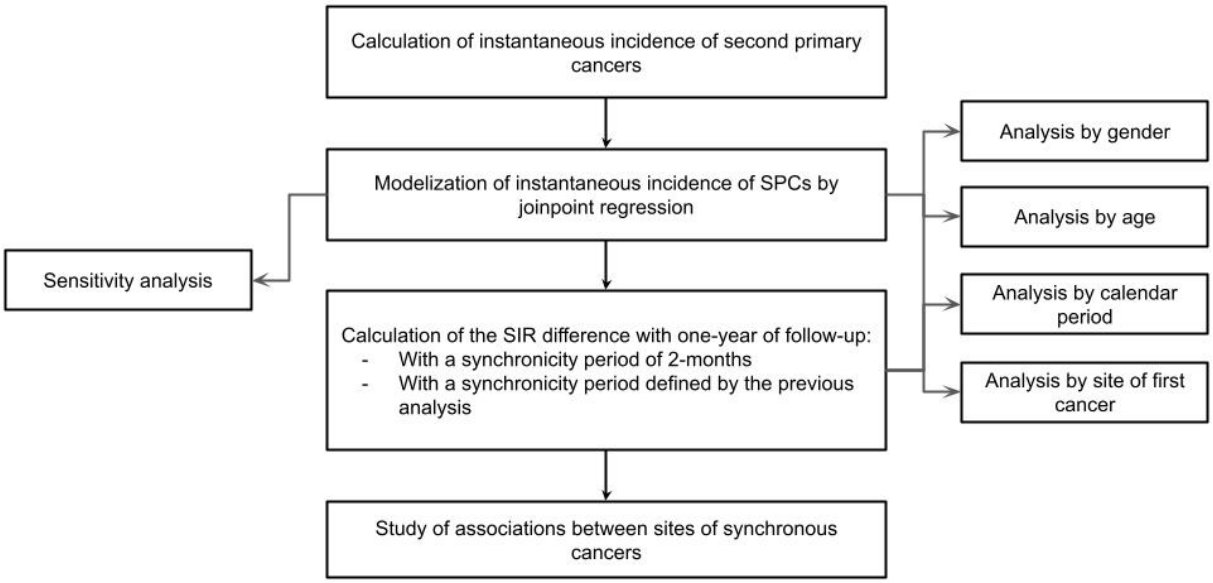
Figure 1: steps of statistical analysis strategy



SPC: Second primary cancer; SIR: Standardized incidence ratio

Figure 2: Joinpoint regression for all sites combined

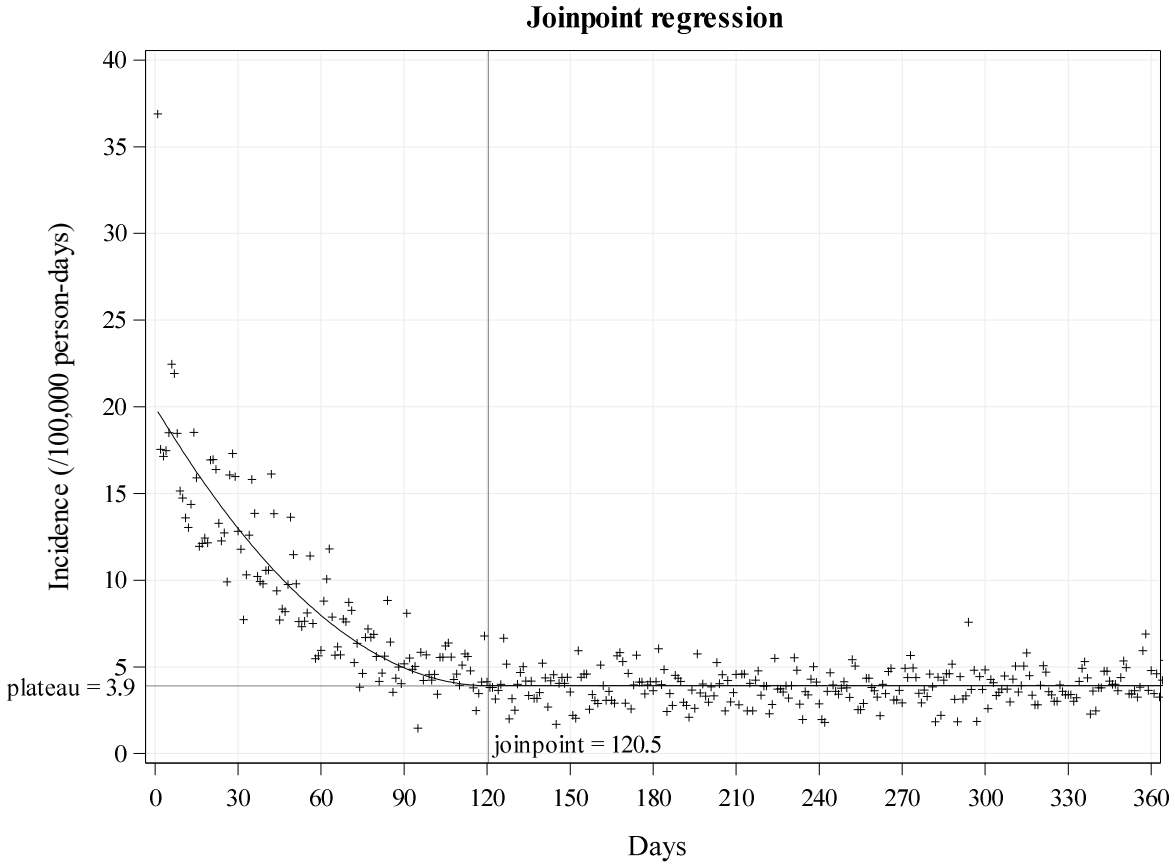


Table 1 : Joinpoint and plateau by gender, age, year of first cancer diagnosis, and site of first primary cancer.

	Characteristic	Joinpoint [a] (days)	95% CI	Incidence plateau (/100,000/day) [95% CI]	Second cancers
All patients		120.5	[112.0-129.0]	3.9 [3.7-4.1]	12,623
Gender	Males	127.8	[118.0-137.6]	5.4 [5.0-5.7]	9,493
	Females	96.1	[87.6-104.7]	2.3 [2.2-2.5]	3,130
Age at first cancer diagnosis (year)	< 45 y	98.3	[74.3-122.3]	1.0 [0.8-1.3]	315
	45 y- 54 y	105.8	[95.2-116.3]	2.5 [2.2-2.7]	1,214
	55 y- 64 y	128.8	[116.6-141.0]	3.6 [3.3-3.9]	2,762
	65 y- 74 y	137.4	[123.6-151.1]	4.9 [4.6-5.3]	4,383
	>= 75 y	105.4	[94.2-116.5]	5.2 [4.9-5.6]	3,949
Year of first cancer diagnosis	1989-1994	105.3	[93.0-117.6]	3.8 [3.5-4.1]	1,654
	1995-1999	95.9	[84.9-106.9]	3.7 [3.4-4.0]	2,215
	2000-2004	122.7	[111.0-134.5]	3.9 [3.6-4.1]	3,385
	2005-2010	142.2	[129.8-154.5]	4.2 [3.9-4.5]	5,369
Site of first primary cancer	Head and neck	102.9	[91.6-114.1]	9.7 [8.6-10.8]	1,307
	Oesophagus	84.7	[75.6-93.7]	6.5 [5.1-8.0]	438
	Colon	92.7	[81.5-103.8]	4.2 [3.8-4.7]	1,017
	Rectum	118.3	[104.8-131.8]	3.8 [3.2-4.4]	723
	Larynx	102.9	[77.8-128.0]	9.6 [8.1-11.1]	364
	Lung, bronchus and trachea	85.0	[72.4-97.5]	4.0 [3.6-4.5]	965
	Breast	93.4	[69.9-116.9]	1.6 [1.4-1.7]	740
	Prostate	203.2	[164.9-241.4]	4.2 [3.8-4.6]	2,131
	Bladder	250.1	[212.6-287.6]	8.1 [5.9-10.2]	1,304
	Kidney	87.2	[55.2-119.3]	6.6 [5.8-7.5]	499
	Non-Hodgkin's lymphoma	85.5	[62.3-108.7]	3.4 [2.8-4.0]	340

[a] The joinpoint is the point from which the risk of SPC becomes constant.

Table 2 : Standardized incidence ratio (SIR) with a synchronicity period of 2 months or 4 months respectively, among patients diagnosed with a first cancer in France between 1989 and 2010.

		Synchronicity period: 2 months				Synchronicity period: 4 months				
	Characteristic	**O** [a]	**E** [b]	**SIR_{2m}** [c]	**95% CI**	**O**	**E**	**SIR_{4m}**	**95% CI**	**ΔSIR** [d]
All patients		7,388	5,152.9	1.43	[1.40-1.47]	5,237	4,015.7	1.30	[1.27-1.34]	-9.1%
Gender	Males	5,497	3,692.9	1.49	[1.45-1.53]	3,851	2,872.4	1.34	[1.30-1.38]	-10.1%
	Females	1,891	1,460.1	1.30	[1.24-1.35]	1,386	1,143.3	1.21	[1.15-1.28]	-6.9%
Age at first cancer diagnosis (year)	< 45 y	179	59.8	2.99	[2.57-3.47]	141	47.4	2.97	[2.50-3.51]	-0.7%
	45 y- 54 y	629	260.9	2.41	[2.23-2.61]	463	205.6	2.25	[2.05-2.47]	-6.6%
	55 y- 64 y	1,572	944.3	1.66	[1.58-1.75]	1,109	741.0	1.50	[1.41-1.59]	-9.6%
	65 y- 74 y	2,651	1,951.7	1.36	[1.31-1.41]	1,854	1,526.3	1.21	[1.16-1.27]	-11.0%
	>= 75 y	2,357	1,936.2	1.22	[1.17-1.27]	1,670	1,495.6	1.12	[1.06-1.17]	-8.2%
Year of first cancer diagnosis	1989-1994	977	671.0	1.46	[1.37-1.55]	732	518.8	1.41	[1.31-1.52]	-3.4%
	1995-1999	1,299	946.4	1.37	[1.30-1.45]	962	734.2	1.31	[1.23-1.40]	-4.4%
	2000-2004	1,979	1,353.6	1.46	[1.40-1.53]	1,393	1,056.6	1.32	[1.25-1.39]	-9.6%
	2005-2010	3,133	2,186.9	1.44	[1.39-1.49]	2,150	1,706.1	1.26	[1.21-1.31]	-12.5%
Site of first primary cancer	Head and neck	665	198.3	3.35	[3.10-3.62]	507	153.3	3.31	[3.03-3.61]	-1.2%
	Oesophagus	143	81.9	1.75	[1.47-2.06]	97	60.4	1.60	[1.30-1.96]	-8.6%
	Colon	555	467.6	1.19	[1.09-1.29]	412	367.0	1.12	[1.02-1.24]	-5.9%
	Rectum	360	309.0	1.17	[1.05-1.29]	229	242.7	0.94	[0.83-1.87]	-19.7%
	Larynx	226	82.2	2.75	[2.40-3.13]	169	64.7	2.61	[2.23-3.04]	-5.1%
	Lung, bronchus and trachea	434	408.6	1.06	[0.96-1.17]	316	30.0	1.04	[0.93-1.16]	-1.9%
	Breast	517	445.2	1.16	[1.06-1.27]	379	355.0	1.07	[0.96-1.18]	-7.8%
	Prostate	1,518	1,148.5	1.32	[1.26-1.32]	1,066	914.3	1.16	[1.10-1.24]	-12.1%
	Bladder	729	239.7	3.04	[2.83-3.27]	418	186.0	2.25	[2.04-2.47]	-26.0%
	Kidney	342	183.7	1.86	[1.67-2.07]	261	143.9	1.81	[1.60-2.05]	-2.7%
	Non-Hodgkin's lymphoma	203	188.4	1.08	[0.93-1.24]	151	157.6	1.02	[0.87-1.20]	-5.6%

[a] O=observed number of SPCs; [b] E=expected number of SPCs; [c] SIR=standardized incidence ratio; [d] ΔSIR=relative difference between SIR at 2 months and SIR at 4 months ($\Delta SIR=(SIR_{4m} - SIR_{2m})/SIR_{2m}$)

Table 3 : Association of sites of synchronous cancers (SC)

Site of first cancer	Persons at risk [a]	Site of second primary cancer [b]	Observed	Proportion [c]	Number of SC all sites	Proportion of SC all sites
Head and neck	26,741	Lung, bronchus and trachea	202	0.76%	801	3.00%
		Oesophagus	195	0.73%		
		Head and neck	173	0.65%		
		Larynx	60	0.22%		
Oesophagus	11,104	Head and neck	139	1.25%	343	3.09%
		Lung, bronchus and trachea	62	0.56%		
		Colon and rectum	33	0.30%		
		Larynx	22	0.20%		
		Liver	19	0.17%		
Colon	50,857	Rectum	103	0.20%	607	1.19%
		Prostate	68	0.13%		
		Lung, bronchus and trachea	67	0.13%		
		Kidney	61	0.12%		
		Breast	51	0.10%		
Rectum	31,567	Colon	162	0.51%	495	1.57%
		Prostate	68	0.22%		
		Lung, bronchus and trachea	46	0.15%		
		Kidney	39	0.12%		
Larynx	8,394	Lung, bronchus and trachea	80	0.95%	197	2.35%
		Head and neck	39	0.46%		
		Oesophagus	28	0.33%		
		Thyroid gland	13	0.15%		
Lung, bronchus and trachea	64,952	Head and neck	92	0.14%	620	0.95%
		Prostate	83	0.13%		
Breast	107,738	All sites	362	0.34%	362	0.34%
Prostate	107,920	Kidney	210	0.19%	1,066	0.99%
		Lung, bronchus and trachea	173	0.16%		
		Colon and Rectum	171	0.16%		
		Bladder	131	0.12%		
Bladder	21,485	Prostate	657	3.06%	888	4.13%
		Lung, bronchus and trachea	73	0.34%		
		Colon and Rectum	35	0.16%		
Kidney	19,922	Prostate	64	0.32%	232	1.16%
		Lung, bronchus and trachea	34	0.17%		
		Colon and Rectum	24	0.12%		
		Haematological cancers	22	0.11%		
Non-Hodgkin's lymphoma	23,193	Lung, bronchus and trachea	31	0.13%	189	0.81%
		Colon and Rectum	27	0.12%		
		Kidney	23	0.10%		
All sites	686,807				7,361	1.07%

[a] Persons at risk=number of persons with a first cancer diagnosis; [b] site of second cancer by decreasing number of observed SC; [c] number of observed SC divided by persons at risk.