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INTERPRETING SURVIVAL DIFFERENCES AND TRENDS

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Since 1990 a concerted action between European population-based cancer registries (the EUROCARE project) has been carried out with the aims of establishing whether there are differences in cancer patient survival in Europe, and the reasons for such differences. Survival differences actually exist for cancer sites for which the stage of disease at diagnosis is the major prognostic factor (such as breast, stomach and colon cancer). However, for most cancer sites, survival increases over time and the survival rates of different countries tend to converge towards higher values. Interpreting survival differences and trends is not an easy task. Longer survival may be achieved by postponing death through better treatment or by anticipating diagnosis. However, an earlier diagnosis may or may not make a treatment more effective in postponing death. The computation of stage-specific or stage-adjusted survival is not sufficient for interpretation of survival differences, because staging procedures change over time and may vary in different hospitals and countries. In addition to an early diagnosis and more effective treatment, a number of factors may bias survival estimates. They may be classified into factors that can be controlled in the analysis (at least partially), such as mortality from other causes, demographic factors, epoch of diagnosis, different statistical methodology, and factors depending on the validity of cancer registry data, such as definition of the illness, exhaustiveness and quality of registration, completeness of follow-up, definition of the date of diagnosis, and definition of disease stage including the diagnostic procedure used to establish stage. To help disentangle the effects of early diagnosis and better treatment, several statistical approaches are being developed: multivariate analysis on relative survival data, new modeling analysis to separately estimate the proportion of cured patients and the length of survival for those patients destined to die, and the standardized collection of information on stage at diagnosis and staging procedures.

Key words: epidemiologic studies, population-based studies, relative survival.

Population-based studies on survival

The aims of population-based studies of cancer patient survival include monitoring the performance and the equity of health care systems, estimating required resources, and establishing priorities for health care investment and research. In 1990, the European Union funded a Concerted Action between all the European population-based cancer registries (the EUROCARE project, European Cancer Registry-based Study of Cancer Patients' Survival and Care) whose major aims were to establish whether there are survival differences among European populations, their extent and reasons for such differences. The EUROCARE working group demonstrated that there are little differences in cancer patient survival among European populations whenever effective treatment is available, such as for testicular cancer and Hodgkin's disease. Conversely, there are major survival differences for cancer sites for which the stage of disease at diagnosis is the major prognostic factor (such as breast, stomach and colon cancer). However, for most cancer sites, the time trend analysis showed that survival length tended to increase over time, and the data from different countries tended to converge towards higher values.[2] An overview of the major EUROCARE results is given in the present issue.[23]

Interpreting survival differences and trends is not an easy task. Reasons for geographical and temporal trends include changing age and general health conditions of the populations, host factors such as genetic and comorbidity factors, different histology, different subsite distribution of tumours within a given organ, stage distribution, diagnostic criteria, equipment and practices, availability of trained oncologists and modern treatment equipment. Most of these determinants are dependent on socioeconomic and cultural factors, such as access to and cost of treatments, supportive care and screening programs, health policy and clinical traditions. The latter have evolved rapidly with the development of clinical trials but are inevitably influenced by presumptions not based on formal scientific evidence, perceived risks *versus* benefits (e.g., small survival advantage at the price of poorer quality of life), uncertainty concerning the interpretation of results of clinical trials, and delay in the communication of trial results and consensus protocols.

Basic logical issues in the interpretation of survival differences

Survival time is the interval between the date of diagnosis and the date of death. Longer survival, may therefore be achieved by postponing death, e.g. through better treatment, or by anticipating diagnosis. However, an earlier diagnosis may or may not make a treatment more effective in postponing death.

An earlier diagnosis may be an early clinical diagnosis, depending on more attention to early symptoms by the physician or the patient himself, or preclinical diagnosis, due to screening programs or incidental discov-

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ery in the course of instrumental examinations made for other purposes. A later death may depend on better treatment or on more effective conventional treatment made possible because of an earlier diagnosis. In observational studies, the distinction between these determinants of longer survival is far from straightforward. The issue is relevant for public health because an early diagnosis without effective therapies may be a disadvantage for the patient.

In principle, one could discriminate if longer survival is due to better treatment or earlier diagnosis (whether accompanied by later death or not) carrying on survival analyses within strata of disease stage. One would conclude that treatment matters only if better survival is achieved for patients with the same disease stage at diagnosis. Conversely, if stage-specific survival were the same, one could conclude that the reason for a better survival was just a more favorable stage distribution. Such conclusions would rarely be justified because of the stage-migration phenomenon.[14] This depends on the evolution of diagnostic practices and on the availability of diagnostic techniques: the same cancer case could be diagnosed as metastatic in one hospital and localized in another, depending on the diagnostic equipment used to discover metastatic dissemination not clinically overt. As a consequence, even if the overall case mix and survival were the same, the first hospital would show better survival performance in localized and advanced stages: its "localized" cases, in fact, are more localized than in the second hospital, because all the cases with silent metastatic spread could be properly classified as advanced; in contrast, its "advanced" stages would also perform better because of the inclusion of less advanced metastatic cases that in the second hospital are still classified as localized.

A new analysis, carried out by the Cox proportional hazard model, on 10-year survival data of 1986 breast cancer patients operated at the Milan National Cancer Institute in 1977-1978 compared to those operated in 1971-1972[5], provides an example of the effect on survival of the stage-migration phenomenon. The overall 10-year survival was found to increase from 60% in the first period to 65% in the second, and node-negative and node-positive patients both showed an improvement of survival of the same magnitude. Table 1 shows (Model 1) that the age-adjusted relative risk (RR) of death for women with metastatic lymph nodes operated in the late seventies with respect to those operated in the early seventies was 0.82, meaning 18% reduction of the hazard rate. By further adjustment for the number of positive nodes (Model 2), this reduction increased up to 30%, corresponding to an age-adjusted RR equal to 0.70, but this would be a biased estimate determined by the stage shifting consequent to the more thorough investigation of axillary lymph nodes. In fact, the mean number of examined axillary lymph nodes during surgery was 6 in the first period and 15 in the second. Adjusting also for the number of examined nodes made, the results reversed. The RR was estimated as 0.94, not significantly different from 1 (Model 3). This example is based on a clinical series and cannot be interpreted as proof of the absence of progress in survival. However, it illustrates the stage migration phenomenon, due to the increased number of axillary nodes resected and histologically examined in two different periods.

Table 1 - Relative risk (RR) of death by Cox's multivariate analysis on 1,235 women with N+ breast cancer treated at National Cancer Institute, Milan, in 1971-72 and 1977-78

Prognostic factors		Model 1 RR	Model 2 RR	Model 3 RR
Period of diagnosis	1971-72[a]	1	1	1
	1977-78	0.82*	0.70*	0.94
Age at diagnosis		1.01	1.01	1.01
No. of metastatic nodes :	1[a]		1	1
	2		1.19	1.17
	3+		2.52**	2.60**
No. of examined nodes:	1-5[a]			1
	6-9			0.60
	10+			0.59*

[a] Reference category; *p<.0001; **p<.005

Several studies have shown that patients included in clinical trials[32] or treated in specialized hospitals or by specialized clinicians[16,30] have longer survival than patients treated elsewhere. We have to consider that those clinicians working in oncologic institutions are more likely to carry out thorough and invasive staging investigation in order to establish the appropriate therapy and enroll patients in clinical trials. In order to exclude selection bias that would derive from the fact that patients with far advanced disease stages may not be referred to specialized centers, a number of studies have carried out stage-specific or stage-adjusted survival analyses, which, however, may actually have increased the bias. A further difficulty in this kind of comparison is that cancer patients with major comorbidity factors may not be referred to specialized cancer hospital and tend to be excluded from clinical trials. This makes the survival statistics of cancer centers and general hospitals generally incomparable.

When due to more effective treatment, a survival increase should be accompanied by a decrease in mortality rates, or by divergent incidence and mortality trends. This is the case for testicular cancer, whose incidence is still increasing in most populations[7], but mortality began to decrease as soon as effective drugs became available in the early seventies. Conversely, the practice of screening and the growing availability of techniques of early diagnosis usually increase incidence. This is the case of prostatic cancer in several countries, where incidence is rapidly increasing and mortality is increasing at a slower pace[9], thus suggesting that the improvement in survival is mainly due to an earlier diagnosis, or to the diagnosis of latent cancer, with little or no effect on the time of death.

A major survival trend towards improvement has been observed for breast cancer before the era of major treat-

ment improvement or screening: the proportion of breast cancer patients surviving at 5 years actually increased from about 50% in the fifties to about 65% in the seventies[29]. Earlier clinical diagnosis leading to more effective conventional treatment is likely to have been the major reason for such an increase. In the United States, in the early eighties, with the widespread use of mammographic screening, breast cancer incidence and survival began to increase more steeply and increased for several years while mortality remained stable[21]; in the early nineties, incidence stopped increasing and the trend actually seemed to reverse, as one would expect if the effect of screening were just to anticipate the diagnosis by a few years. At present, mortality rates are also decreasing[31], suggesting that the practice of early clinical and preclinical diagnosis is also affecting the effectiveness of treatment and hence the time of death. A similar decrease in breast cancer mortality in recent years has been observed in the United Kingdom[25]; however, it is too early to be a direct consequence of the organized mammographic screening started in the early nineties. Mortality is also decreasing in Italy, especially at young ages. This might be due to better oncologic treatment or to earlier clinical diagnosis, but also to a decreasing incidence in young generations[4,24].

We have recently shown that mortality rates for lung and laryngeal cancer in Italy diverge, in the sense that the curve for lung cancer is plateauing whereas that of laryngeal cancer is dropping. Since the tumours share several etiologic factors (i.e., tobacco and occupational risk factors), such a diverging mortality trend is not likely to be due to diverging incidence trend. It is more likely due to a diverging survival trend, which is increasing for laryngeal and stable for lung cancer. There is evidence that lung and laryngeal incidence trends were parallel[3]. This helped us to interpret with confidence the observed survival trend for laryngeal cancer patients as due to more effective treatment.

Metodologic issues in survival comparison

Such intrinsic difficulties of survival interpretation are made more complex by a number of methodologic problems and biases whose presence and size must be accurately evaluated before any simplistic interpretation of survival differences. A more extensive review of the potential biases in survival comparison has been published elsewhere[1]. Methodologic problems affecting survival estimates can be classified in two groups: A) factors that can be controlled in the analysis (at least partially); 1) mortality from other causes, 2) demographic factors (age at diagnosis and sex of the patients); 3) epoch of diagnosis; 4) different statistical methodology; B) factors depending on the validity of cancer registry data; 5) definition of the illness and its evolution over time; 6) sensitivity (exhaustiveness) and specificity (quality) of registration; 7) completeness of follow-up; 8) definition of the date of diagnosis. Several examples, taken from the EUROCARE experience[2], which may be also helpful in interpreting the ITACARE data[33], are discussed.

1) Mortality from other causes

Mortality from causes other than the cancer at issue is a factor that can heavily bias survival comparisons, especially among older patients. Survival of cancer patients of a different sex and age, or in different countries and/or time periods, may be affected by different competitive mortality (i.e., death for causes other than that under study). This issue is usually addressed through the computation of relative survival, i.e., the ratio of observed survival to the expected survival for the general population of the same age and sex, and alive in the same calendar years as the cases. Relative survival is an estimate of what would have been the survival of cancer patients in the absence of causes of death other than their cancer. The appropriateness of life tables to compute the expected rates is of crucial importance because in several countries, including Italy, general mortality has been rapidly changing in recent years[22]. In principle, to compute the expected rates, instead of total mortality one should use total mortality excluding mortality due to the cancer under study. However, the latter is usually limited and its inclusion only slightly affects the computed relative survival. Table 2 shows the effect of the correction given by 5- and 10-year relative survival in the two sexes, in Varese (northern Italy) and Ragusa (southern Italy) (the example refers to colon cancer data

Table 2 - Five-year and ten-year observed and relative survival (%) for colon cancer in Varese and Ragusa cancer registries, by age class and sex - ITACARE study

Varese		15-44		45-54		55-64		65-74		75+	
		obs	rel	obs	rel	obs	rel	obs	rel	obs	rel
Men	5-yr	52	53	50	52	39	43	33	44	18	35
	10-yr	47	48	44	49	32	41	18	35	8	38
Women	5-yr	48	48	50	51	49	51	45	51	23	36
	10-yr	41	41	42	44	43	48	34	48	13	39
Ragusa		**15-44**		**45-54**		**55-64**		**65-74**		**75+**	
		obs	rel	obs	rel	obs	rel	obs	rel	obs	rel
Men	5-yr	57	58	43	44	39	42	27	34	10	19
	10-yr	57	59	29	30	32	38	13	21	8	35
Women	5-yr	38	39	61	62	43	44	37	42	22	37
	10-yr	38	39	61	64	43	48	26	38	8	31

from the ITACARE study[33]). The correction is clearly higher for elderly than for younger patients, where observed and relative survival figures are very close; it is stronger for men than for women and, in general, more evident at 10 years than at 5 years from the diagnosis. Among middle-aged men, the correction is higher in Varese than in Ragusa because for men the general mortality is higher in the northern than in the southern area. However, for several cancers, the correction for competitive mortality through the relative survival procedure may be insufficient. This is the case of cancers heavily dependent on risk factors also influencing other causes of death, and to which only a fraction of the general population is exposed. Lung cancer, for instance, depends on smoking, which also affects incidence and mortality from other cancers, cardiovascular diseases and chronic obstructive pulmonary disease. To properly compute relative survival for lung cancer patients, one should refer it to the expected survival of smokers (or, better, of a theoretical population with the same distribution of risk factors as the lung cancer patients). The survival of the exposed population would be lower than the general population which is generally used; consequently the relative survival of cancer patients would be higher.

2) Demographic factors (age at diagnosis and sex of the patients)

Young cancer patients usually live longer than elderly patients, even after excluding death from other causes, directly or through computation of relative survival. Female patients also tend to show higher relative survival rates than males (Table 2). Most of these demographic differences depend on different stage distribution. Any geographical comparison, therefore, requires statistical adjustment to take into account different age at diagnosis and sex distribution. For this purpose, the sex and age-adjusted relative survival can be calculated from the sex and age-specific rates[34]. As standardized incidence or mortality rates, this index expresses relative survival for a hypothetical set of patients with a previously defined age structure. Simultaneous adjustment for two or three factors, such as age, sex, or period of diagnosis, is often needed. In this case, a conventional standardization procedure may give very unstable estimates, due to the small number of subjects available for each combination of levels of the considered factors. An alternative approach for comparing relative survival rates can be then based on multiple regression models (see also next point 4 on statistical methodology). Adjusted figures may be applied to a cancer patients standard used as reference[33]. Table 3 shows the effect on the ranked 5-year relative survival by the multivariate approch (sex, age and period of diagnosis adjustment) for stomach cancer patients of the Italian registries participating in the ITACARE study[33]. The 5-year relative survival in Latina ranked first in the crude approach and sixth in the adjusted approach (relative survival figures being 30% and 21%, respectively). In fact, cancer patients in Latina are younger than those of both other Italian centers and the EUROCARE cancer patient group, used here as standard.

Table 3 - Ranked 5-year relative survival for Italian cancer registries[a] participating in ITACARE by crude and multivariate approach. Stomach cancer, 1986-89

Crude relative survival[b]		Rank	Sex and age-standardized relative survival[g]	
Latina[f]	(30%)	1	Forlì-Ravenna	(27%)
Varese	(28%)	2	Varese	(24%)
Forlì-Ravenna[d]	(26%)	3	Modena	(24%)
Modena[e]	(25%)	4	Parma	(23%)
Genova[d]	(24%)	6	Latina	(21%)
Firenze[c]	(23%)	5	Firenze	(22%)
Parma[f]	(21%)	7	Genova	(20%)
Ragusa	(17%)	8	Ragusa	(17%)

[a]5-year relative survival in parentheses; [b]Both sexes combined; [c]1985-87; [d]1986-88; [e]1988-89; [f]1986-87; [g]Relative survival adjusted by age, sex and period of diagnosis by Estève's model, and standardized on a distribution of European cases by age and sex.

3) Epoch of diagnosis

With a few exceptions, the age-specific survival of cancer patients increases over time, because of progressive improvements in early diagnosis and/or treatment. Survival comparisons between populations, therefore, must be time specific. However, in several cases, decreasing trends have been observed. In EUROCARE, for instance, in a few countries cervical cancer survival decreased over the study period; this was likely due to the selective prevention of less aggressive tumours through cytologic screening. In the Netherlands, a decreasing survival trend for pharyngeal and laryngeal cancer has been interpreted as due to changing subsite distribution, with more supraglottic and hypopharyngeal cancer, whose prognosis is worse and stage at diagnosis more advanced than glottic and other pharyngeal cancers[6].

4) Different statistical methodology

Observed survival is the cumulative probability of surviving at a given time after diagnosis, irrespective of the cause of death. It is based on all deaths actually observed. However, this survival probability should be considered as the result of two components, depending on the mortality from the disease under study and, respectively, from all other causes considered together. *Net survival* can be defined as the survival that would be observed if the risks of death from causes other than the cancer under study were removed[13]. During the follow-up, net survival probability tends to become constant as deaths due to cancer decrease. Two classical methods are available for estimating net survival: the method of *cause-specific survival,* in which death from other causes is considered as the end of follow-up, and that of *relative survival.* Unfortunately, information on specific cause of death is generally lacking or unreliable in population-based studies and the *cause-specific survival* is not usually available. Relative survival is the alternative measure aimed to correct survival val-

ues for competing causes of death. Relative survival is computed as the ratio of the survival observed for the considered group of patients to the survival expected for the same age and sex distribution in the general population. Various methods for calculating relative survival differ in how expected survival rates are computed. The method of Ederer et al.[10] derives expected survival as the proportion of survivors that one would expect in a group of subjects belonging to the general population with the same age and sex distribution as the patients under study at the start of follow-up, i.e., at the time of diagnosis. However, the approch does not take into account that the general mortality of the population may change with time, becoming progressively different from that considered at the start of follow-up (in several European countries, general mortality decreased dramatically in the last decades[22]), and that the aging of patients changes their life expectancy[11]. The Hakulinen method[18,19] calculates relative survival estimates corrected, at each follow-up time-interval, for aging of patients and for changes in the reference general mortality levels. However, due to their worse life expectancy, elderly patients are selectively removed from the study group, so that their expected survival progressively approaches that of young patients[17]. A method which takes into account this further specific effect is available[12].

The Registry of Geneva, Switzerland, systematically verifies and corrects if necessary the causes of death of the recorded cancer patients. It is therefore able to carry out cause-specific survival probabilities. An exercise on 5-year follow-up of cases incident in 1970-1977 in Geneva for a number of cancer sites (i.e., stomach, colon, lung, breast, prostate, ovary and bladder cancer) showed that cause-specific survival figures were almost systematically higher than relative survival figures, particularly for stomach, lung and bladder cancer, for which relative survival was underestimated by about 15-20%[13]. These results can be explained by the fact that the relative survival method does not delete those deaths resulting from the undesirable effects of treatment or, more importantly, from diseases provoked by the same risk factors as the cancer[13].

Assuming proportional hazards, the prognostic independent value of factors affecting observed survival is generally estimated by the Cox[8] multiple regression model. With a similar approach, a *multiple regression model* can be used to fit *relative survival* rates, i.e., the extra risk of death due to cancer, as a function of a number of explicative factors. The Hakulinen method[20] is designed to deal with aggregated survival data, cross classified according to the levels of the considered prognostic factors. Since follow-up time is formally treated in the same way as the other explicative factors, the proportional assumption can be released in the Hakulinen approach by introducing the appropriate interaction terms in the regression model. The method of Estève et al.[12] works with individual survival data. The computer program available to fit the Estève model assumes proportionality of cancer death risk across the levels of the different factors. However, in this case, an exact probability of non-cancer death is calculated for each subjects and each subperiod of follow-up.

5) Definition of the illness and its evolution over time

In addition to stage and treatment, definition of the illness and the case mix within the broad cancer categories that are usually compared (e.g., the ICD 3rd digit codes) is likely to be the most important factor influencing and biasing survival comparisons. Laryngeal cancer, as well as oral, oropharyngeal and hypopharyngeal cancer, include a mix of different clinical entities with different etiology and prognosis. For instance, in the countries where laryngeal cancer incidence is high, as in southern Europe, supraglottic lesions are more frequent than glottic lesions. Conversely, in northern Europe, most laryngeal cancers are localized in the glottis. Supraglottic and glottic tumours have different prognoses because the latter give early symptoms whereas the former are usually diagnosed when far advanced[15]. EUROCARE showed that laryngeal cancer patients had a longer survival in northern countries than in southern Europe, but this probably reflected a different subsite frequency than better performance of the health care system. In EUROCARE, the ratio between glottic and supraglottic cancer was 4 in Germany, 3 in UK, 2 in Denmark and The Netherlands, 1 in Switzerland and Italy, and 0.6 in France. As regards the oropharynx, where cancers arising in the tonsil have a better prognosis than other subsites, the proportion of tonsil cancer ranged from about 80% in UK, Denmark and Germany to about 40% in France and Italy. For the hypopharynx, the proportion of cancers of the pyriform sinus, which have a worse prognosis than cancers of the postcricoid and other regions, ranged between over 85% in France and Switzerland to less than 60 in UK. Unfortunately, most registries lack subsite information for too many cases to permit proper comparison.

6) Sensitivity (exhaustiveness) and specificity (quality) of registration

The validity of cancer registration, i.e., its sensitivity (exhausiveness) and specificity (reliability of diagnosis) is likely to be a determinant of the validity of population-based survival comparison. Population-based cancer registries aim at registering certain standardized clinical information, including the clinical and pathologic diagnosis, its date and the date of death, for all cancer cases occurring in a given population. However, several cases are usually missed. The major indicator of the exhaustiveness of cancer registration is the proportion of cases that would not have been registered if not notified by death certificate (the so-called death certificate "initiated" [DCI] or notified [DCN] cases). In fact, a large proportion of DCI indicates that the clinicopathologic sources of information are incomplete and that also alive patients may have been missed. Many cancer registries attempt tracing back the DCI cases in hospital

or administrative files or through general practitioners in order to collect at least some clinical data, notably the date of diagnosis, which is essential for survival analysis. The cases for which the death certificate remains the only source of information (the so-called "death certificate only" [DCO] cases) are usually excluded from survival analyses. The exclusion of DCO determine a selective loss of fatal cases. This implies that cancer registries with a given proportion of DCI and a high proportion of DCO overestimate their survival rates with respect to registries with the same proportion of DCI and a lower proportion of DCO. In the EUROCARE Project, the size of the DCI-DCO bias was evaluated for the Thames cancer registry (UK), where the proportion of DCO was fairly high (25% for lung cancer, 22% for colon cancer, 11% for breast cancer). Tracing back the DCO cases considerably reduced the estimates of survival: 5-year crude survival rates decreased from 6.4% to 4.8% for lung cancer (25% reduction), from 33.3% to 26.6% for colon cancer (20% reduction), and from 60.1% to 54.1% for breast cancer (10% reduction). The proportion of DCO cases excluded from the analysis approximately indicated the proportional reduction of survival estimates that would have been caused by their inclusion. Most likely, however, the true survival lies somewhere in between the two estimates, because a high proportion of DCO suggests that long-term survivors may also have been missed[28]. Within ITACARE[33] the proportions of DCO are much smaller than those considered here, usually less than 5%; the corresponding bias, therefore, is likely to be trivial.

Another major bias of survival comparison may arise when the quality of the diagnostic information is poor, e.g., when histologic diagnosis is lacking. A relatively high survival rate of pancreatic cancer, for instance, may depend on the inclusion of false-positive cases in the incidence series. In EUROCARE study[2], pancreatic cancer survival was very low for Switzerland (2-3% at 5 years), with a very high proportion of histologically confirmed cases, and relatively high for Poland (5-6%), suggesting that some benign lesions were erroneously included.

7) Completeness of follow-up

Follow-up must be complete to avoid major biases in survival estimation. Patients lost to follow-up are likely to be different from those under control. In clinical series, a major reason for loosing track of the patients is actually their death. In population series, the major reasons are linkage errors (e.g., because of different spelling of the names in cancer registries and in death files) or migration (several registries lack facilities to follow-up patients abroad). EUROCARE survival estimates for Switzerland, for instance, are slightly overestimated because immigrants with uncurable cancer tend to return to die in the country of origin[26]. For some cancer sites, e.g., for stomach cancer, the true survival may be as much as 5% lower than the estimated survival.

Conversely, linkage errors may determine considerable overestimation for those registries that rely only on passive follow-up in countries without reliable personal identification numbers. EUROCARE estimated the potential size of the bias through an active follow-up survey of long-term survivors of highly lethal cancers to detect diagnostic and follow-up errors. Four registries carried out an active follow-up of 482 lung cancer cases believed to be alive at 5 years after the diagnosis and discovered that 88 of them were actually dead and their death was missed. The observed survival rate changed from 7.2% to 5.9%. The size of the error can be expressed as the proportion of dead cases that were erroneously registered as living, i.e., 1.4%. For a lethal tumour such as lung cancer, this caused a 22% overestimate of survival, but, for less lethal tumours, errors of this magnitude would affect survival estimates to only a minor extent and can be considered acceptable in most cases. In the case of breast cancer, for instance, such an error would change survival estimates by less than 1%.

8) Definition of the date of diagnosis

Different cancer registries use different definitions of date of diagnosis, that is the index date to compute incidence and survival rates, namely the date of first clinical diagnosis, the date of first hospital admission, the date of first pathologic confirmation and, in a few cases (not in Italy), the date of first treatment with a curative purpose. The time interval between these dates may vary from a few days to a few months, but is not likely to affect long-term survival estimates and comparisons. In EUROCARE, using different index dates for survival computation for lung and colon cancer resulted in survival estimates at 5 years that differed by less than 2%.

Towards the interpretation of survival differences and trends

In addition to describing and comparing properly computed survival data, the major aim of survival analysis is to understand the reasons for survival differences: whether they are due to different disease stage at diagnosis (i.e., early versus late diagnosis) or to different treatments. In the former case, the question is whether they depend exclusively on lead time (i.e., just early diagnosis without later death), or whether an early diagnosis also makes conventional treatment more efficient, thus leading to postponement of death. Within EUROCARE this aim was pursued through 3 different strategies:

- 1st) Multivariate analysis of survival at different time intervals from the date of diagnosis. For colon cancer, for instance, the analysis of 68,283 incident cases diagnosed in 1978-1985 in 12 European countries proved that most of the survival differences between countries were confined to the first 6-month period following diagnosis: the relative risks of dying in the first 6 months ranged from 0.8 to 2.9, whereas the relative risks conditional to having survived 6 months ranged

from 0.9 to 1.7. This suggests that the most important determinant of survival differences is the proportion of advanced cases at the time of diagnosis, although some treatment effect cannot be excluded[27]. A similar ongoing analysis of 119,139 cases of breast cancer suggests that early diagnosis and treatment may both be of importance to explain international differences, the latter especially in young women.

• 2nd) Mixed model analysis of the two major components of survival: the survival function of the patients that are bound to die of the disease and the proportion of cured patients (i.e., patients whose survival does not differ from that of the general population). The presence of the latter subgroup is evidenced in many cases by the flattening of the relative survival function, sometimes after diagnosis, at a value different from zero. Explicative covariates such as age and stage at diagnosis and treatment may play a different role on the proportion of cured patients and on the death rate for fatal cases, potentially facilitating the interpretation of survival differences. In preliminary analysis of the EUROCARE data set for colon cancer, for instance, age appeared to be inversely associated with the relative survival of colon cancer patients through both components, but the pattern of association appeared different. The proportion of cured patients markedly decreased with age up to 55 years and it remained almost stable for the subsequent age classes. Conversely, results suggest that the excess mortality of fatal cases presents a slight increase up to about age 60 and a very steep increase later on.

• 3rd) Stage-specific or stage-adjusted comparisons on samples of incident cases (EUROCARE High Resolution Studies). For these cases the participating registries collect further information on stage at diagnosis, staging procedures actually performed (such as number of lymph nodes histologically examined to search for metastasis, imaging techniques for distant metastasis) and treatment. The information on diagnostic and staging procedures is essential for unbiased stage-specific comparisons. When survival increases in localized and advanced stages, in fact, it could be concluded that treatment is improving, but the same effect could be due just to an improvement of diagnostic procedures, which may shift the classification of cases from the localized to the advanced stage category, thus apparently improving the prognosis of both. The example of the study on breast cancer treated at the Milan National Cancer Institute highlights this problem (Table 1). Population-based studies on colonic, rectal, breast, and stomach cancer are presently ongoing in the frame of the "high resolution" Eurocare project; information has been collected on samples of cases diagnosed in the early nineties.

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