programmes to prevent and detect cancer at an early stage. The advantages of having the registry outweigh the difficulties and problems we have in operating the registry successfully.

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Estimating the Incidence of Cancers in Switzerland: 1983–1987

L. Raymond, J.L. Bulliard, F. Levi, F. Enderlin, A. Méan, G. Schüler and J. Torhorst

Estimates have recently been made of the incidence of cancers in the countries of the European Community. Similar estimates are given for Switzerland, based on data from the six Swiss cantonal cancer registries, all of which have been operating for at least 12 years. These registries cover Basel, Geneva, Neuchatel, St Gall and Appenzell, Vaud and Zurich, which account for about 50% of the Swiss population as a whole. Two different methods were used to extrapolate from the incidences observed in the regions covered by cancer registration to the entire country. The first method is based solely on the distribution of populations according to the country's main linguistic groups, whereas the second relies on mortality data. Estimates obtained by the second approach are presented and their reliability is discussed. Comparison of the age incidence curve with that of Denmark tends to confirm the validity of the estimations. Estimated standardised rates (world population) for all sites except non-melanomatous skin cancer are 294.3 for males and 214.2 for females. Comparisons with other European countries show that in males, lung cancer is relatively less common in Switzerland, whereas in females, breast cancer is relatively more frequent.

Key words: cancer incidence, Switzerland, methodology, EC
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INTRODUCTION

IN SWITZERLAND, about 30% of deaths in males and 25% of those in females are attributed to cancer. These figures are obtained from death certificates which are collected by the Swiss Federal Statistical Office. Numbers and rates of incident cases would be useful in order to enable international and interregional comparisons, to monitor trends over time, to provide essential background for aetiological research as well as to evaluate prevention efforts. Such information is available only in regions covered by cancer registries whose primary objectives are to monitor incidence.

Nonetheless, it is possible to make estimates of the number of new cases occurring in an entire country through careful use of data combined from all the areas "covered" by registries. The accuracy of such estimates depends on the extent to which the areas of cancer registration are representative of the whole

Table 1. Size of the resident population, % employed in agriculture and indicators of quality of cancer registration in the six Swiss regions covered by a registry, and considered in the report

Canton/region	Population*	% employed in agriculture†	% of cases histologically verified‡	Incidence/mortality ratio‡
Basel (city and country)	420 866	1.2	90.8	1.7
Geneva	369 803	0.7	92.3	1.8
Neuchatel	155 424	3.6	89.4	1.6
St-Gallen and Appenzell	462 241	7.0	93.8	1.8
Vaud	536 094	5.2	89.9	1.7
Zurich	1 128 673	2.0	89.7	1.8
Total	3 073 101	3.1	90.8	1.6
% whole Switzerland§	47.4	28.5	—	—

*Average yearly resident population in 1983–1987 estimated by the Swiss Federal or the Cantonal Statistical Offices. †Percentage of the labour force (according to the national Census of 1980). ‡All sites combined, excepting non-melanomatous skin cancers, period 1983–1987. §Percentage of the whole resident and of the farming population in the Swiss cantons covered by cancer registries; the latter percentage was 5.3 in 1980 for Switzerland as a whole.

country. Several series of countrywide estimates have been published [1–4], including one [4] focused on the member countries of the European Community. For each of them, incidence was estimated using a regression equation derived from regions covered by tumour registries.

Two simplified methods were used to extrapolate cancer incidence from areas of cancer registration to the whole of Switzerland. Both methods attempt to take into account the possible lack of representativeness of the regions covered. Estimates obtained by one of these approaches are presented and discussed.

MATERIALS AND METHODS

In Switzerland, the first comprehensive cancer registration scheme began in 1970 in the canton of Geneva. Five others were subsequently established during the following decade. Together, they cover the populations of the cantons of Basel (both City and Country), Geneva, Neuchatel, St. Gall and Appenzell, Vaud and Zurich. All were set up in response to local needs and interests rather than as a part of an overall plan to provide information for the country as a whole. Although the registration areas include four of the five largest cities in the country, somewhat less than half of the Swiss resident population is presently covered. As a consequence of an over-representation of urban areas, populations engaged in agricultural activities are thus under-represented. Furthermore, there is an imbalance in the representation of the Swiss linguistic communities: 58% of the French-speaking population is represented while the proportion of the German-speakers is 43% (Table 1). Therefore, aggregated incidence data cannot simply be extrapolated to the country as a whole.

The number of registered cases was provided by the six registries, according to year of incidence, sex and 5-year age groups. The number of cancer deaths for the same groups was obtained from the Swiss Federal Statistical Office. Estimates of the resident population of the cantons were also available through the same office as well as from the corresponding statistical services operating in each of the six cantons providing incidence data.

Incidence data for the whole country have been estimated by two different methods using mortality and/or incidence data.

The first method (hereafter also referred to as method 1) relies only on incidence data. It utilises data obtained from the German- and French-speaking cantons covered, and simply extrapolates to the totality of the population of the same linguistic group. For a particular linguistic age and sex group, if p represents the proportion covered by the tumour registration scheme, and if P is the total population, then the estimated number of cases is given by the product of the observed cases and the ratio P/p. Calculations were made, given the simplifying assumption that the entire population of each of the 25 Swiss cantons belongs to the linguistic group of the local majority. For the purpose of this study, the canton of Tessin, the only one in which the majority of the population speaks Italian, was grouped with the French-speaking cantons.

The second method (hereafter also referred to as method 2) uses both incidence and mortality data but, unlike method 1, does not take into account the linguistic distribution of the population. For each tumour site and age and sex group, it is assumed that the ratio of incidence to mortality is the same throughout the country. For each age-sex subgroup considered, if c and d are, respectively, the number of cases and the number of deaths observed in the population covered by registries, and if D is the number of deaths observed in the entire country, the number of incident cases is estimated as the product of c and D/d. When the number of deaths (d) was 0 in one of the sex and age groups, the number of corresponding incident cases was also set to 0 (but due to grouping of cancer sites such a situation remained relatively rare).

The estimates presented are those for the calendar period 1983–1987 so that they may be compared with data recently

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published for other countries [5]. In order to avoid classification problems which could arise from combining mortality and incidence data, tumour sites have been partially grouped, according to the Eigth Revision of the International Classification of Diseases (ICD-8), which has been in use for mortality statistics in Switzerland since 1969 [6]. The age and sex structure of the population allows calculations of standardised rates for the country as a whole. Such calculations can in fact be made independently of the method of extrapolation used.

RESULTS

Estimates obtained by the two methods were comparable. For all sites combined, the estimated yearly numbers of new cases of cancer were 13 500 versus 13 800 for males and 12 400 versus 12 200 for females using methods 1 and 2 respectively as described above. The differences observed did not follow the same trend for various tumour sites. For males, estimates derived from method 1 compared to those of method 2, were lower for cancers of the lung and upper respiratory and digestive tract, as well as for the stomach, whereas the pattern was reversed for colorectal, pancreas and bladder cancers. For females, estimates for lung and upper respiratory and digestive tract sites were higher with method 1 than with method 2 as are those for breast and genital cancers, whereas estimates given by method 1 were lower for cancer of the stomach.

Summary figures derived from the second method are presented in Table 2. Estimated numbers of cases have been rounded to the nearest 10 or 100 for three and four digits estimates respectively. Overall, it was estimated that about 26 000 new cases of cancer occurred in Switzerland each year during the 5-year period 1983–1987. Of these, less than half (12 200) occurred in females. In fact, differences in incidence between the sexes appeared more clearly when the comparisons were based on rates, since they depend on the size of the corresponding population at risk. After correcting for the difference in age structure between the two sexes (the female population being older) according to the world population, age-standardised rates were 35% greater in males than in females.

Age-specific rates for all sites combined showed that the risk of cancer progressively increased from the age of 15 right through to the oldest age groups. This age-related risk increased more rapidly for males than for females. The overall increase in risk with age is nearly identical to that reported for Denmark which has a national registration system [5] (Figure 1). In contrast, the age-related increase in rates in France, as estimated by an approach essentially identical to that of our method 2 is, particularly starting from around ages 60 to 65 years, considerably less pronounced than that noted in our country [3].

DISCUSSION

Several methods have been proposed for the estimation of the incidence of cancer in populations where new cases are not systematically registered. The most complex ones are based on a combination of mortality and survival data; in theory, they allow one to reconstitute successive annual cohorts of incident cases in different age groups [7]. Most other approaches limit themselves

*Table 2. Estimated annual number of new cancers and corresponding incidence rates for Switzerland as a whole**

Cancer site (ICD-8)	Number of cases		Standardised rates†	
	Males	Females	Males	Females
Oral cavity, pharynx and larynx (140–9, 161)	860	170	20.2	3.0
Oesophagus (150)	250	NE	5.3	NE
Stomach (151)	760	510	15.6	6.7
Colorectum (153–4)	1700	1600	34.8	23.4
Liver (155)	270	NE	5.7	NE
Pancreas (157)	370	370	7.7	5.4
Digestive sites, total (150–9)	3600	3000	73.6	42.5
Lung (162)	2500	470	55.3	8.4
Skin, melanoma (172)	380	480	9.3	10.1
Breast (females) (174)	—	3500	—	66.1
Uterus, total (180–182)	—	1200	—	23.9
Ovary (183)	—	650	—	11.9
Prostate (185)	2500	—	46.8	—
Testis (186)	310	—	8.6	—
Genital organs, total (M:185–187; F:180–184)	2900	2000	56.9	38.1
Bladder (188)	690	260	14.6	3.7
Kidney (189)	470	290	10.2	4.8
Nervous system, total (191–2)	260	180	7.3	4.4
Non-Hodgkin's lymphoma (200,2)	460	370	10.6	6.2
Hodgkin's disease (201)	120	80	3.1	1.9
Myeloma (203)	160	160	3.3	2.4
Leukaemias (204–8)	410	330	9.7	6.8
Total, all sites (140–208 173)‡	13 800	12 200	294.3	214.2

NE, not estimated. *Period 1983–1987; estimates based on "method 2". †Age-standardised rates per 100 000 on the world population. ‡All sites combined, excepting non-melanomatous skin cancers.

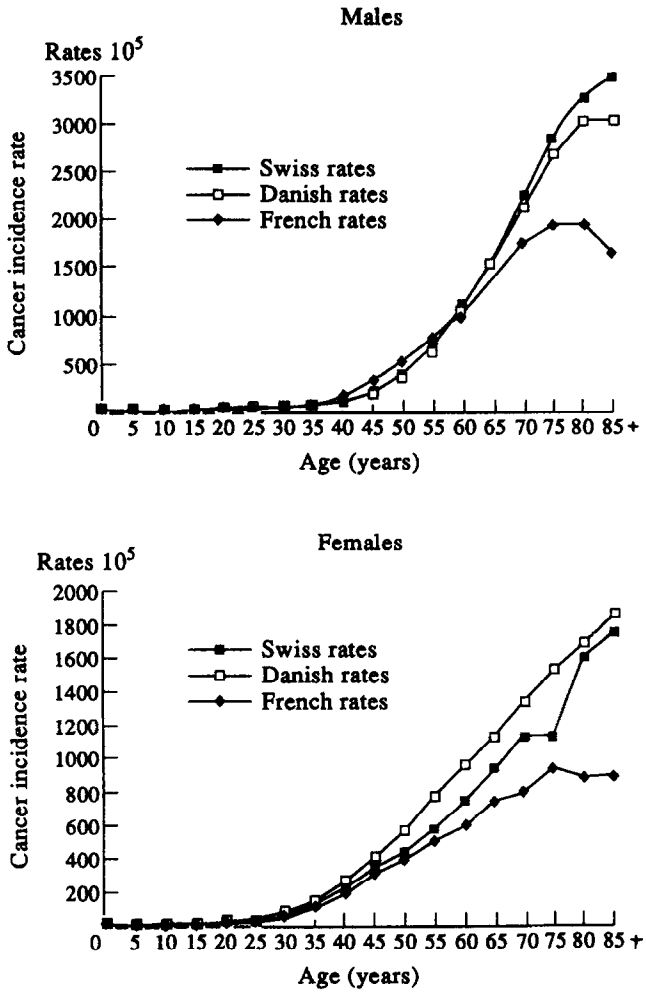

Figure 1. Average yearly age-specific cancer incidence rates for all sites combined (except non-melanomatous skin cancers): comparison between incidence curves observed in Denmark (1983–1987) and those estimated for the whole Swiss (1983–1987) and French (1978–1982) populations.

to estimates based on the relationship between mortality and available incidence figures, but different approaches have been proposed [1–4]. In France, incidence/mortality ratios based on data accumulated from five departments out of 78 were applied to the nation as a whole, for each site, sex and age group. The results thus obtained were compared with information actually collected in a "control department" and, accordingly, were considered as relatively reliable by the authors. This is the approach (our method 2) on which we finally settled in order to derive estimates for Switzerland. The method used to estimate incidence in the member countries of the European Community [4] determined, for each site, the best predictive function which could be derived from incidence–mortality data. This approach assumes that the relationship between incidence and mortality varies between regions or between countries. If cancer cases are less efficiently treated and followed up in "predictor regions" than in "estimated regions", overestimates of incidence will result [4]. In Switzerland, the quality of care and follow-up is generally considered to be satisfactory, even in rural areas. In this situation, it is therefore likely that survival rates do not differ widely among regions; consequently, the use of an incidence–mortality ratio obtained by pooling available data should not introduce any appreciable bias. In applying our method 2, we did not find it necessary to use, as a basis for calculations, different periods for incidence and mortality data. This is in contrast to the estimation methods used by the European Community [4], where an average interval of 2 years between the two sources of information was used, so that incidence and mortality data would, in fact, apply to approximately the same cohort. For Switzerland, failure to take into account this "methodological precaution" would not appreciably influence incidence estimates, since currently there are no major time trends in either incidence or mortality patterns (one exception worthy of mention may concern carcinoma of the stomach for which 1-year survival remains particularly poor).

It must be emphasised that all methods which make simultaneous use of mortality figures and of incidence and/or survival data obtained from registries may be affected by bias due to inconsistencies between the cancer site noted at the time of diagnosis and that recorded as the underlying cause of death. It is difficult to know if this inconsistency results in over- or underestimation of incidence, especially since the reliability of death certification may vary from one region to another. Our method 2 would be as vulnerable as any other to such bias. Indeed, previous Swiss studies have revealed divergences between the underlying cause of death noted on death certificates and the site noted by the registry, or even between the cause noted on the death certificate and the cause noted by the registry [8]. Nonetheless, according to these validity studies, such divergences would not lead to any appreciable systematic errors, since they occur in opposite directions and thus tend to cancel each other out. In particular, it is reassuring to note that the results obtained from the two methods considered in this report are generally comparable, and that the slight differences between the estimates may be reasonably interpreted as due to linguistic and geographical differences in the distribution of the most recognised or suspected risk factors for cancer. For example, it is not surprising that method 1, at least in comparison to method 2, "underestimates" the incidence of lung cancer among males and "overestimates" the incidence in females. This is due to the fact that our registries "over-represent" the large cities, where trends in lung cancer incidence resulting from decreased consumption of cigarettes in males and from increased consumption in females are beginning to emerge. It is also not surprising that the incidence of gastric cancer, still relatively higher in some rural areas, is "underestimated" by method 1, which extrapolates from urban areas to the country as a whole. The opposite phenomenon is noted for colorectal and female breast cancers, which are known to be more frequent in urban populations. On the whole, these observations provide some reassurance as to results obtained by method 2, in spite of the potential problems mentioned above concerning the consistency and quality of information available on death certificates. The high level of medical services in Switzerland and the percentage of cases which are histologically verified (Table 1) are indicators of the accuracy of the information concerning tumour sites.

Another point in favour of the method which was finally adopted in this report is that it provides a convincing and consistent trend in age-specific incidence. The striking similarity between our "calculated" curve and the one actually observed in Denmark, whose system is widely recognised for its consistency and reliability, tends to confirm the high standard attained by cancer registration in Switzerland. As concerns the French data, which were estimated by the same method [3], it is difficult to interpret the dip in the incidence curve after the age of 75 other than by supposing that it may be due to under-registration of

cases in the elderly in the regions from which the overall estimates have been extrapolated. As data from France are for a 5-year former calendar period, this comparison may be somewhat approximate.

The comparison of the incidence estimates presented in this report with recently published data [5] allows us to rank Switzerland in relation to other European countries, especially those of the European Community, which are represented by no fewer than 43 national or regional cancer registries. Approximately half of these regions are of southern Europe and France; the others are situated in central and northern Europe. Such geographical distribution thus covers a large spectrum of cultural behaviours which may influence cancer rates. As far as overall incidence rates are concerned, Switzerland is in the upper half of the distribution, ranking 13th for males and 15th for females (although rankings tend to vary according to individual cancer sites). For cancers linked to alcohol consumption, such as those of the oral cavity, Switzerland occupies an intermediate rank (21st) for males and a lower one for females (34th). The incidence of stomach cancer is in the lower third of the distribution for both sexes (31st and 32nd, respectively), and that for colorectal cancers is somewhat higher (22nd and 28th, respectively). Cancer of the pancreas is relatively frequent (15th and 9th highest, respectively). Over the period covered by this study, Switzerland had a relatively favourable lung cancer ranking (28th and 25th, respectively). In contrast, the country is in an unfavourable position as regards cancers of the breast (9th), prostate (first), and cutaneous melanomas (first rank in both sexes). For the two latter cancers, however, the Swiss rank may be explained in terms of a high detection rate.

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MDM2 Gene Amplification in Human Breast Cancer

B. Quesnel, C. Preudhomme, J. Fournier, P. Fenaux and J.-P. Peyrat

The MDM2 gene is a gene whose product binds to p53 and regulates its functions. The amplification of the MDM2 gene has been found in one third of human sarcomas, and a differential expression of MDM2 gene in relation with oestrogen receptor status was recently found in human breast cancer cell lines. We analysed 60 breast cancers for MDM2 gene amplification by Southern blot. This event was observed in 1 case with high levels of oestrogen receptor (ER). Thus, MDM2 gene amplification seems to be a rare event in breast cancer. Further studies are needed to define precisely the relationship between MDM2 amplification and ER status.

Key words: MDM2, gene amplification, breast cancer, oestradiol receptor
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THE p53 gene is a tumour suppressor gene whose inactivation through point mutations and/or deletion is frequent in solid tumours [1]. In primary breast cancer, about 20% of the cases have a p53 gene mutation [2, 3].

Although inactivation of p53 usually results from point mutations, other mechanisms of inactivation of this protein may occur in human tumours. One of those recently identified results from over-expression or amplification of the MDM2 gene. The gene was originally isolated from a tumorigenic mouse fibroblast cell line containing double minutes, a cytogenetic hallmark of gene amplification [4]. Over-expression of the MDM2 gene in cells increases their tumorigenic potential. Binding of the 90-kD MDM2 protein to the p53 protein inhibits the p53-mediated transactivation of a gene with a p53-responsive element [5]. Moreover, the p53 protein can transactivate MDM2 gene expression in an autoregulatory feedback loop [6]. The fact that