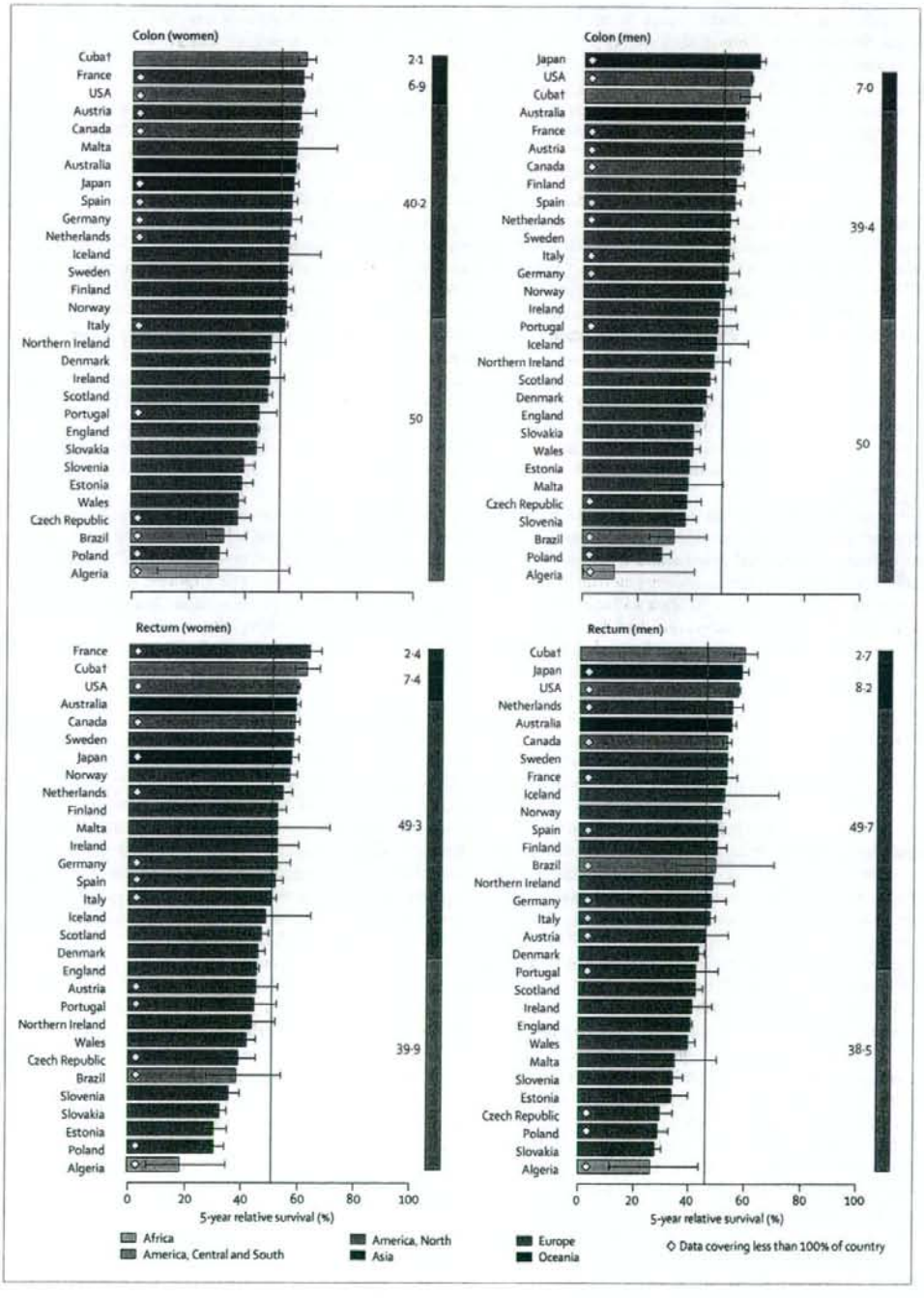

Figure 3: **5-year relative survival (%), age-standardised to the ICSS weights* with 95% CIs for adults (aged 15–99 years) diagnosed with cancer of the colon or rectum during 1990–94 and followed up to Dec 31, 1999: country**
Vertical bar on the right of each graphic shows the contribution (%) of each continent to the total number of cases analysed (contributions under 1% are not labelled). Red vertical line represents mean survival for the 22 European countries that participated in EUROCARE-3, age-standardised to the ICSS weights. *Age-standardised to ICSS weights, except for Sétif, Algeria (all cancers), Austria (rectum [women]), Iceland (rectum [men and women]), Ireland (rectum [women]), Malta (colon [men] and rectum [men and women]), which were unstandardised values (see text). †Problems with data quality might have led to over-estimation (see text).

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in each sex, although 782 (36%) patients had been excluded as DCO (available online[w]).

In Canada, the pooled estimate of 5-year survival was 58·7% for women and 53·1% for men, slightly lower in the global range than for cancers of the breast, colon, or prostate in Canada. Survival in men ranged from 51·1% (Ontario) to 64·6% (British Columbia), and from 57·8% to 62·8% in women. In the USA, 5-year relative survival for all races combined was 56·9% in men and 59·8% in women, with a range from 46–67% in men and 52–66% in women (table 2 and figure 2). Again, most of the estimates were within a narrow range, from 55–60% in men and 57–62% in women. By contrast with colon cancer, survival from rectal cancer was slightly higher in women than in men.

5-year survival for rectal cancer in the USA was generally lower for blacks than for whites, in both sexes (webfigure 4). The overall estimate of 5-year survival in men was 47·4% for blacks and 57·3% for whites; for women, the estimates were 49·4% for blacks and 60·4% for whites (table 3). When survival for blacks was above 60%, or higher than for whites in the same population (Colorado, Connecticut, Nebraska, Rhode Island), the estimates for blacks were based on around 50 or fewer patients, with wide CIs, and were usually not age-standardised (table 3 and webfigure 4). Even where blacks comprised 25% or more of the population (Atlanta, GA, Detroit, MI, New York City, NY, Louisiana), 5-year survival was 6–16% lower than for whites in the same area. The pooled estimate of 5-year survival in areas covered by NPCR was 56·3% for men and 58·8% for women, some 2–3% lower than for SEER areas (58·5% men, 61·8% women; table 3 and figure 2).

5-year survival ranged from 46·2% to 67·9% in whites; in blacks, the range of age-standardised survival was from 42·8% to 63·5% (table 3 and webfigure 4). Survival in blacks was generally lower than the mean value for all included US populations, although more often within the control limits. Survival for whites was also generally within the control limits, with the exception of New York City, NY, where survival was below the control limits (webfigure 3).

In Japan, the pooled survival estimate for colon cancer was 58·2% for men and 57·6% for women, although survival was lower in Osaka (54–55%) than in Fukui or Yamagata (60–64%; table 2 and figure 3).

In Europe, the geographical pattern for age-standardised 5-year survival was similar to that for colon cancer. For men, the range was from 28–30% in Poland, West Bohemia (Czech Republic), and Slovakia to 53–55% in France, Sweden, and the Netherlands; whereas for women, the range was from 30–32% in Poland, Estonia, and Slovakia up to 63·9% in France, where three of the four contributing registries ranked the highest in Europe (table 2 and figure 3). The pooled estimates for the 51 contributing registries in 23 European countries were 43·2% in men and 47·4% in women. Data on rectal cancer were not available for Isère (France), northern Netherlands, or the five Swiss registries. 5-year survival in Ireland was 41·1% in men and 52·5% in women. The estimate for women is not age-standardised, but it is based on over 200 patients (table 1), and similarity between the raw and standardised estimates for cancers of the colon and colon and rectum combined (less than 1%, data not shown) suggests that an age-standardised estimate for rectal cancer would not have been very different. In Northern Ireland, the estimates were 48·2% in men and 43·8% in women (pooled UK estimates were 40·6% in men and 45·3% in women; table 2).

The national estimate of age-standardised 5-year survival for rectal cancer in Australia was 54·8% in men and 59·2% in women. Survival ranged from 45–57% in men and from 55–61% in women.

Of 663621 men with prostate cancer, 35934 (5%) were excluded for a previous cancer, leaving 627687 eligible first, primary, invasive cancers of the prostate (available online[w]). After 11163 (2%) exclusions for DCO, 1640 (<1%) for autopsy-detection and 801 (<1%) for major error, 614083 men were included in the analyses (98% of those eligible). Of these, 403000 (66%) were resident in North America, 162000 (26%) in Europe, and 43000 (7%) in Australia (table 1). Microscopic verification was available for 96% of the tumours. Less than 1% of men were censored from the analysis within 5 years of diagnosis, but 3·2% died within 1 month of diagnosis.

5-year relative survival, age-standardised to the ICSS weights, ranged from 80% or higher in the USA (92%), Canada and Austria to less than 40% in Denmark, Poland, and Algeria (table 2 and figure 1).

The 5-year survival estimate of 21·4% (95% CI 8·7–38·9) in Sétif (Algeria) was based on 36 patients, and was not age-standardised.

In Brazil, 5-year survival was 34·4% in Campinas and 55·7% in Goiânia. Some 30% of tumour records in Campinas were excluded with major errors. Notably, 20 (13·4%) men in Campinas and 71 (21·8%) men in Goiânia died within 1 month of diagnosis, which are the highest proportions of any of the participating registries (available online[w]). 5-year survival in Cuba was 69·7% (table 3). This estimate was based on 4300 patients, but 54% of the original data set of 9500 patients had been excluded as DCO (table 1 and data available online[w]).

The pooled estimate of 5-year survival for prostate cancer in Canada was 85·1%, ranging from 77·5% in Saskatchewan to 89·3% in British Columbia (table 2 and figure 1). In the USA, 5-year relative survival from prostate cancer was 91·9% for all races combined, with a range from 81·6% in New York City, NY up to 95·0% in Seattle, WA (table 2 and figure 2), but most of the estimates were within a fairly narrow range, from 88·6% (Louisiana) to 94·0% (Atlanta, GA). The relative survival estimate for the state of Michigan was 100%, although in the city of Detroit, MI, with 42% of the state population (webtable), survival from prostate cancer in the same period was 93·8%.

Age-standardised 5-year relative survival for prostate cancer in blacks was lower than for whites in all

populations for which this could be separately assessed with race-specific life tables (webfigure 2). The overall estimate of 5-year survival was 85·8% for blacks and 92·4% for whites, with an overall difference of 6·6% (table 3). The difference in survival between blacks and whites ranged from 5·0% (Florida) to 14–16% (Nebraska, Rhode Island), and although the largest differences arise where the black populations are smallest, each survival estimate was based on at least 70 patients (webtable). Survival in whites ranged from 83·3% (New York City, NY) to 96·1% (Atlanta, GA), and in blacks from 74·0% (New York City, NY) to 89·6% (Seattle, WA). The pooled estimate of 5-year survival was 89·5% in areas covered by NPCR, and 93·1% in SEER areas (table 3).

Survival in blacks was usually lower than the pooled US estimate, and often more than three standard deviations below it, after controlling for precision (webfigure 3). Survival in whites was generally within the control limits. 5-year survival for whites was above the upper 99·8% control limit in three SEER populations (Atlanta, GA, Seattle, WA, and Detroit, MI). Survival in whites was below the lower control limit in four NPCR populations, but for California and Florida the difference was small (2–3%). In New York State, including New York City, NY, survival estimates are precise, but 6–9% below the pooled US estimate of 92·3% and well below the lower control limit (webfigure 3).

The 5-year relative survival estimates for Michigan State (100% in both blacks and whites) were too high, and they are not shown in webfigure 3, although the data were included in the pooled estimate. Information about the death had not been linked to the tumour record for some of the apparent 5-year survivors from prostate cancer in Michigan State, leading to an inflated estimate. This error did not affect the survival estimates for prostate cancer in Detroit, MI or those for other cancers in Michigan State.

The pooled estimate of 5-year survival in Japan was 50·4%, much lower on the global scale than for cancers of the breast, colon, or rectum in Japan. Survival estimates were similar in all three prefectures (table 2 and figure 1).

The range of 5-year survival in Europe was especially wide for prostate cancer, from less than 40% in Poland and Denmark to more than 80% in Austria (table 2 and figure 1). The pooled estimate for the 49 contributing registries in 23 European countries was 57·1%. Data were not available for nine registries: Switzerland (five registries), Isère and Côte d'Or (France), Granada (Spain), and northern Netherlands. 5-year survival in the Ireland was 62·8%. In Northern Ireland, the estimate was 54·0%, slightly higher than the pooled estimate of 51·1% for the UK (table 2).

The national estimate of age-standardised 5-year survival for prostate cancer in Australia was 77·4%. Survival was closely similar in the six largest states, in the range 76–80%, but notably lower in the two smallest regions: 63·7% in Northern Territory (based on 78 patients, estimate not age-standardised) and 70·2% in Tasmania (1321 patients).

Discussion

To our knowledge, the CONCORD study is the first attempt to provide directly comparable data on cancer survival from many countries around the world by use of central quality-control procedures, standard analytic methods, and a single, centralised analysis of individual tumour records from population-based cancer registries. The findings should eventually complement the international data series on cancer incidence[63,64] and mortality[65–67] that have been available for several decades. Cancer-mortality statistics have often been used for international comparisons of progress against cancer,[68–72] but they are also affected by well-known problems of comparability, both between countries and between successive revisions of the ICD.[73–75] The findings presented here should help joint consideration of trends in incidence, survival, and mortality as indicators of cancer control. None of these indicators is perfect, but none is adequate on its own.[76–78]

Around 2800 life tables were created to enable the estimation of relative survival by age, sex, country, and race.[46] The life tables are available on the CONCORD website.[34]

5-year relative survival for breast, colorectal, and prostate cancers was generally higher in North America, Australia, Japan, and northern, western, and southern Europe, and lower in Algeria, Brazil, and eastern Europe.

Exclusions for a previous cancer (5–9%) were not unexpected. Population-based cancer survival analyses are usually restricted to patients with a first, primary invasive cancer, therefore, to the extent that patients with a previous cancer have been completely excluded in this study, this improves the comparability of the findings with other studies. Participating registries began operation between 1950 and 1990. The data from newer registries are more likely to include unrecognised second and subsequent cancers, because any previous cancer(s) in a given patient might have been diagnosed before the registry began operation.

The main indices of data quality for cancer survival are the proportions of registered patients known to the registry by DCO, or lost to follow-up, and histologically verified. Data quality varied between registries (available online[34]), but was high overall: very few records were excluded with a major error. Exclusions for major errors were high in Campinas, Brazil (26–47%). The overall proportion of patients who died within 1 month of diagnosis was low for breast cancer (2·3%) and prostate cancer (3·2%), but higher for colon (10·9%) and rectal cancers (7·8%). These values varied between registries, but the overall pattern is plausible; up to a third of colorectal cancers present as an emergency with bowel obstruction. Fewer than 1% of patients were censored from the analysis within 5 years of diagnosis.

Three registries were excluded after quality control, because of high losses to follow-up or inefficient regional or national linkage of information on the deaths of patients with cancer. The data for three other registries, Cuba, Campinas (Brazil) and, for prostate cancer, Michigan State

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(USA), are less reliable than those from other registries, although for different reasons, discussed below. As with the first global compilation of cancer incidence data, in the 1960s, retention of the two registries from Central and South America was partly prompted by the paucity of information on cancer survival from that region: "in this situation, even incomplete data have value".[54]

Overall, the exclusion of DCO registrations accounted for only 1% (9215) of the eligible records for breast cancer, 3% (13 102) for colon cancer, 1% (3213) for rectal cancer, and 2% (11 163) for prostate cancer (available online[34]). The percentage was less than 1% in Algeria, USA, Canada, and Australia, and in the range 0–5% in most European countries and in Brazil, but higher in Osaka (Japan; 5–22%),[79] south Thames (UK); 10–16%), and Cuba (28–60%).[80]

The proportion of DCOs is not particularly useful as a comparative index of data quality,[81] but a high proportion of DCO records does suggest that routine data-collection systems might not be complete. The relevance of this index also varies with the system of data collection. Sweden does not use DCOs because the registration of patients with cancer at the time of diagnosis is close to 100%; by contrast, hospitals in Cuba are not allowed to retain the clinical records of deceased persons for more than 5 years.[80]

The different proportions of DCO records are unlikely to explain the differences in survival between Europe and North America, however. The survival of patients whose tumour is registered as a DCO is generally lower than the mean for all registered cancer patients,[82] so if they could have been included, the transatlantic differences in survival would have been slightly greater. Furthermore, most DCO records in the European data are for patients aged 75 years or over,[43] where the survival differences are in any case more marked.[5] By contrast, if a high proportion of DCO records is taken to suggest under-registration of long-term survivors, this might produce lower survival estimates. Adjustment for both DCOs and incompleteness of registration in Thames (UK) and Finland had surprisingly little effect on survival, however, even when 10–20% of registrations were DCOs, because the two corrections tended to off-set one another.[83] Under-reporting of incident tumours by up to 5% has been shown not to affect international comparisons of survival greatly.[84]

A plateau was imposed on the relative survival curve at some point during the first 5 years after diagnosis in about 7% of the 6500 age-specific survival estimates by registry, cancer, sex, and race (data not shown). The effect on the age-standardised survival estimates at national level was almost always less than 1%.

Diagnostic variability between pathologists might contribute to international differences in cancer survival. Thus, survival from colorectal cancer in Japan is among the highest reported here, especially for men. In western countries, invasive colorectal carcinoma is diagnosed when neoplastic tissue invades beyond the submucosa of the bowel. Severe cytological or architectural changes confined to the mucosa (in situ or intramucosal carcinoma) have no metastatic potential, and are often labelled high-grade dysplastic adenoma. Japanese pathologists rely more on cytological features, however, and do not consider evidence of invasion into the submucosal layer as a mandatory requirement for the diagnosis of colorectal carcinoma.[85] Pathological practice on this issue might vary substantially between western pathologists. Islands of dysplastic tissue might also be displaced or herniated beyond the muscularis mucosae without implying invasive potential (pseudo-invasion), and differential diagnosis can be very difficult.[86,87]

Assessment of the extent to which international survival differences might be attributable to differences in the pathological definition of disease would need blinded review of pathological diagnoses of a sample of patients by an international panel of expert pathologists. Such reviews are invaluable, but rare.[88]

Survival in Sétif (Algeria) was the lowest of all the populations in the CONCORD study for each cancer. Even though the dataset was small, and covers only 4% of the national population, there is little doubt that survival in Algeria is very low. The age distribution of patients was younger than in most populations (available online[34]) and it cannot explain the low overall survival. Survival in Sétif was similar to or even lower than survival in blacks diagnosed during 1993–97 in Harare, the Zimbabwean capital, where the very low survival was attributed to inadequate access to facilities for early diagnosis, clinical investigation, and treatment.[89]

Survival in the two Brazilian registries was generally low, although rectal-cancer survival in Goiânia was close to the European mean. Data quality issues prevented the inclusion of data from three of the 20 population-based registries in state capitals: these registries should be used to provide a broader picture of cancer survival in Brazil. Relative survival reported here for patients with cancer diagnosed in Cuba during 1990–94 was about 20% higher than estimates for those diagnosed during 1988–89, just a few years earlier.[80] Cancer survival for children diagnosed in Cuba during 1988–89 was lower than in more developed countries.[90] The high proportion of DCOs in the 1988–89 data was considered less likely to be biased with respect to survival than in other registries, because of the way data were collected,[80] but the survival estimates for Cuba reported here are still likely to be considerably inflated, and should be interpreted accordingly.

National estimates of survival for patients with cancer diagnosed in Japan during 1993–96 were slightly higher than the estimates for 1990–94 reported here.[79] They were based on data from seven prefectures, including the three reported here (Yamagata, Fukui, and Osaka). As in the CONCORD data, survival in Osaka was generally lower than the mean survival for Japan.

Variation in survival between the provinces of Canada and the states and territories of Australia was generally small, and overall survival was high: this suggests health care of a high standard in most areas. Variation between the countries of Europe was much wider.

The substantial differences in survival between Australia and the UK have been noted before.[91] They are unlikely to be because of differences in data quality. For breast cancer, survival from both localised and regional disease was higher in Australia, but survival from metastatic disease was similar. Elderly women in England had especially poor survival. More effective treatment in Australia is a plausible explanation.[92]

Comparisons of cancer survival between Europe and the USA since 2000 have identified wide differences, with survival usually higher in the USA.[9] Closer assessment of these differences with more detailed data, not routinely collected by all registries, has enabled the explanatory effect of clinical variables such as stage at diagnosis, investigative approach, anatomical site, and morphology to be quantified for colorectal cancer[12,93] and breast cancer,[10] and for a range of cancers in children.[11] In those studies, the USA has always been represented by data from the SEER Program registries, representing some 10% of the US population at that time, because no other data have been available. The availability of data from a large number of state-wide population-based cancer registries that began operation around 1990, and meet data quality standards comparable with those of the SEER registries, now enables a larger proportion of the US population to be included in national and international comparisons of cancer survival. The CONCORD study provided the first opportunity for the cancer registries of 11 US states in the NPCR to follow up all their patients for vital status and to undertake analyses of cancer survival, and 42% of the US population is included in these analyses.

The survival differences between US and European patients with cancer, especially in the oldest patients, seem unlikely to be attributable to artefacts of cancer registration. The CONCORD study has nonetheless identified two methodological issues that probably do explain some of the well-known differences in survival between Europe and the USA, from which only SEER data have been available until now.

First, relative survival was about 2–4% higher in SEER-9 areas than in participating NPCR areas of the USA. Consequently, cancer survival in the 42% of the US population covered by the CONCORD study was 1–3% lower than survival in the SEER areas alone (10% of the US population). Direct estimation of cancer survival for other areas of the USA would be desirable.

Second, census-derived US national life tables give higher estimates of all-cause mortality than are noted in the SEER areas, especially with the gradual decline of mortality in the decade after a census.[46] Use of census-derived national life tables to estimate relative survival (the SEER approach) therefore produces estimates that are almost always higher than those obtained with state-specific life tables for each calendar year in the decade (CONCORD approach), which we believe to be more appropriate because it provides tighter control for changes over time in background mortality. With the CONCORD approach, age-standardised 5-year survival in the 22 participating areas of the USA was up to 3% lower than with the SEER approach for breast cancer in women, up to 4% lower for colorectal cancer, and up to 5% lower for prostate cancer (available online[14]).

The differences in cancer survival between blacks and whites of both sexes in the USA are large, and remarkably consistent in 16 states and six metropolitan areas—more populations than it has been possible to study in the past.[94] The differences were adjusted for age and for differences in background mortality between blacks and whites within each state or metropolitan area. It would be interesting to know if the differences were attributable to artefact, or differences between blacks and whites in tumour biology, in stage at diagnosis, in access to health care, or in compliance with treatment. The survival differences seen in this study are consistent with those in other studies.[95–98] Data-collection systems were identical for all races. The black–white differences in relative survival that we report would have been even larger if we had used race-specific national life tables instead of race–state life tables, because background mortality is higher (and expected survival lower) in blacks than in whites in all the populations studied.[23,55]

Survival from cancers of the breast, colorectum, and prostate varied with the type of health insurance in a population-based study:[96] survival was highest in patients who had private insurance, intermediate with federal insurance, and lowest with no insurance. Another study[97] suggested that prostate cancer is not more biologically aggressive in blacks than whites. Late stage,[98] less treatment, and higher mortality seem to be associated with black race, low socioeconomic status, and poor survival in the USA.[99–101] Extensive reviews have led to the conclusion that racial disparities in cancer treatment, which are not explained by clinical factors, lead to worse outcomes in blacks.[102,103] Analysis of SEER data suggested that some racial differences in treatment and cause-specific survival persist after adjustment for poverty.[104] By contrast, the racial difference in survival from colorectal cancer was almost absent in patients managed under the equal-access, integrated health-care Veterans' Affairs system.[105] Finally, overviews of race, socioeconomic status, and cancer outcomes strongly suggest that equal treatment yields equal outcome, irrespective of race.[51,106] The data presented here extend the evidence that cancer survival in the USA is lower in blacks than in whites.

Simple ranking of countries by overall survival can be misleading. Survival is very similar in many European countries, at the centre of the global range, and a small shift in the survival estimate in either direction can entail a large change in the rank. Thus, even the national survival estimates for Iceland and Malta have wide confidence intervals and unstable rankings because they are based on populations of around 250 000 (figures 1 and 3). The detailed data by country and region are tabulated by continent, country, and region, rather than ranked: some

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estimates, based on sparse data, could not be age-standardised (table 2).

The numbers of patients included in the analysis varied widely, as did the proportion of the national population covered by the data. These proportions affect the extent to which the survival estimates can be deemed representative of the country concerned. For example, in Algeria, Brazil, and Germany, only 1–4% of the national populations were covered by the data. Population coverage of participating registries in Italy was about 15%, but they were concentrated in the wealthier north of the country.[22,30] The same point also applies to the USA, however, because the data presented here confirm suggestions[107] that cancer survival in the SEER Program areas (10% population coverage during the 1990s) was higher than in other parts of the country. By contrast, regional variation in survival in Australia and Canada was much less marked than in the USA. Similarly, survival for 1990–94 in the four French départements reported here (6% national coverage) was high on the European scale for most cancers,[27] and a much larger study for the same period in 14 départements (20% coverage) showed similar patterns of survival.[108,109]

For countries with more than one contributing registry but less than 100% population coverage, we have presented estimates of survival derived from the pooled data, not weighted means of the regional estimates of survival. The question of whether pooled survival estimates derived from regional registries with less than 100% national coverage can properly be considered representative of cancer survival in the whole country has been discussed elsewhere.[23] If population-based estimates of cancer survival are deemed reliable, however, they do suggest a potentially achievable level of survival, irrespective of whether the estimate is for a whole country or only one region in that country. Regional variation in survival within a country tends to prompt efforts to improve survival in regions where it is low. The same argument should apply on an international scale. This has already happened in Europe.[110]

No overall worldwide estimate for cancer survival has been presented. The proportionate contributions from each continent to the CONCORD study are very different from the worldwide distribution of cancers of the breast, colon, rectum, and prostate. The national data for Australia alone represented 63% of the population of Oceania in 1995,[111] and the survival estimates for North America included 44% of the combined populations of USA and Canada around 1992, but for Africa, Asia, and South America, the population coverage of these data was much lower. The survival data for Europe were based on 25% of the continental population of 512 million in 1992,[112] but the EUROCARE study (ongoing since 1989) is the largest and most widely cited international study of cancer survival, and all 57 cancer registries in that study, and six others, contributed to CONCORD. To provide an international summary measure of cancer survival for visual comparison, we therefore used the overall estimates for 23 countries in EUROCARE-3, but age-standardised to the ICSS weights used in CONCORD, instead of the weights used in EUROCARE-3.[113] We have presented pooled estimates of survival for Europe and North America (table 3), but not for other continents.

The size of the population covered by the data affects the statistical precision of the survival estimates. This is shown by 95% CIs, but ranked graphics do not provide visual appreciation of the extent to which the survival estimate for a given country or region falls outside the distribution of survival estimates that might be expected, under the hypothesis that survival should be the same in all areas. In that situation, regional variation in relative survival should arise only from random variation around some underlying average. We used funnel plots[62] to provide that visual effect for geographical and racial variation in survival in the USA, with the target value as the pooled estimate for the USA, age-standardised to the ICSS weights.[60] These plots display striking geographical and racial variation in survival.

Clinical practice has continued to evolve in the 15 years or so since the patients included in this study were diagnosed. Changes in diagnosis, screening, and treatment have undoubtedly improved the prognosis for cancer patients, at least in wealthier countries.

Survival has increased substantially for cancers of the breast (women), colon, rectum, and prostate in the 17 areas of the USA covered by the SEER Program during 1996–2003,[114] and in Canada (1996–98)[115] and Australia (1994–2004).[116,117] Smaller increases have been reported in 11 of the 47 Japanese prefectures.[118] These estimates of relative survival, published for national purposes, cannot be compared with the data reported here, however, because of differences in the quality control of incidence data or completeness of follow-up, and in methods of analysis. Some estimates were not age-standardised for international comparison, whereas others were standardised to country-specific age weights, rather than the ICSS age weights that we used.

The only recent international study of cancer survival is EUROCARE-4, which included patients diagnosed in 23 countries during all or part of 1995–2002 and followed up to 2003.[29,30] Survival increased substantially in eastern European countries, where it was much lower than in other parts of Europe during 1990–94. This narrowing of the east–west gap suggests substantial improvements in cancer care. The rise in breast cancer survival in several countries was associated with a fall in mortality, possibly because of improved care and screening programmes; the rise in prostate-cancer survival (and incidence) might be a result of more widespread PSA testing. In western Europe, survival in the UK and Denmark was still low for several cancers in the late 1990s.

CONCORD is, by chance, reasonably well-timed to provide a baseline for international comparisons of cancer survival to assess the effect of several major public health initiatives for the control of breast,

colorectal, and prostate cancers. In 1990, mass population screening for breast cancer with mammography was beginning in many (but not all) participant countries. At that time, intense early diagnostic activity with prostate-specific antigen (PSA) had recently become widespread in the USA, but was little used elsewhere. In Denmark, for example, the 50-year increase in prostate cancer incidence is considered real,[119] but the Danish Society for Urology assessed the evidence in 1990[120] and decided not to advocate PSA testing in asymptomatic men, because the therapeutic benefit was very small;[121] only symptomatic patients were offered treatment. Mass screening for colorectal cancer with faecal occult blood (FOB) testing or endoscopy had not begun during 1990–94 in any contributing country as far as we are aware. Opportunistic screening with the FOB test began in Japan in 1992; by 2004, about 20% of people aged 40 years or over had been tested within the previous year.[122] Opportunistic endoscopy had already become widespread in some parts of the US population by 1990.

The CONCORD study was planned in three phases. The study reported here (phase I, low resolution) was designed to quantify international differences in population-based relative survival by age, sex, country, or region for patients diagnosed during 1990–94 with a cancer of the breast, colon, rectum, or prostate. Phase II (high resolution) was designed to help interpret those international differences in survival, by use of a subset of registries that could re-abstract detailed clinical data, including stage at diagnosis and treatment, from the original medical records for large random samples of patients diagnosed with one of the same cancers during 1996–98. Findings will be reported in due course. Phase III was designed as a blinded, expert review of the pathological diagnosis for a subset of patients from the phase II study, to assess the extent to which international survival differences might be attributable to differences in the pathological definition of disease in participating countries.

The range of survival estimates for each cancer is very wide. Population-based cancer registries are increasingly important in the comparative assessment of cancer outcomes,[123] and even allowing for differences in data quality or statistical robustness, there is little doubt that the chances of survival after a cancer diagnosis vary hugely on a global scale.

The comparability of cancer survival estimates between countries is criticised far more often than the comparability of cancer incidence data from the same registries. There is no statistical basis for this distinction. National sensitivities about cancer survival seem to be much greater than sensitivities about cancer incidence. Cancer survival is a measure of the overall effectiveness of cancer treatment services, whereas cancer incidence is a measure of the long-term effect of prevention policies, which are less visible on a day-to-day basis and can, incorrectly, be seen as less important.

Cancer survival is a valuable indicator for international comparison of progress in cancer control,[76,124,125] despite the fact that part of the variation in cancer survival identified in this study could be attributable to differences in the intensity of diagnostic activity (case-finding) in participating populations. Notably, the very same point applies to international comparisons of cancer incidence. If over-diagnosis—which depends on diagnostic intensity—is more marked in one country than another, then it will certainly be harder for researchers to compare incidence, mortality, and survival in those countries. But over-diagnosis has different connotations for health-care systems and patients. In each country, the health-care system will have to be funded, staffed, and equipped to cope with the diagnostic and therapeutic burden of all patients with cancer, however they are diagnosed. The health-care system must make provision accordingly, and monitor the outcome of that provision; cancer survival is one such overall indicator.

Furthermore, a patient with cancer is still a patient with cancer, whether or not they represent over-diagnosis. If it were possible to distinguish the one from the other reliably, it would be done routinely. As it is, a cancer diagnosis represents the best that medicine has to offer in a given country at a given time, and that best is variable. PSA testing for prostate cancer is an example. No matter how a patient with cancer is diagnosed, they have to cope with the consequences, both psychological and physical, and will usually want to be treated. Such patients cannot be excluded from either incidence or survival analyses. We do not know who they are. In this sense, cancer incidence and survival estimates describe as accurately as possible the occurrence and the outcome, respectively, of cancer as it is diagnosed and treated at a given time in a given population.

Most of the wide global range in survival is probably attributable to differences in access to diagnostic and treatment services.[3,82,89,91,126] International variation in survival in Europe has been associated with national levels of economic development, as measured by total national expenditure on health.[29] Survival is positively associated with gross domestic product and the amount of investment in health technology such as CT scanners.[124] Part of the international variation in survival is thus probably attributable to under-investment in health resources.[127,128] The variation in survival might be considered intuitively obvious, given wide global variation in expenditure on health care, whether that is expressed in absolute terms or as a proportion of national resources. A parallel could be drawn with differences in survival between rich and poor patients with cancer in a given country, which have frequently been reported.[129,130]

Until now, however, direct international comparisons of cancer survival between high-income and low-income countries have not generally been available. The information provided here might therefore be a useful stimulus for change.

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Contributors
All authors were involved in the study design. JML, MPC, GG, and MSant undertook the pilot study. RC, SF, RdA, MSantaquilani, MQ, GG, MSant, FB, JML, TH, SK, and AV were involved in data preparation and quality control. MQ, RdA, BR, FB, PB, TH, JLY, and MPC did the data analyses. MPC, FB, JLY, TH, HW, JML, MQ, BR, RdA, AM, PB, JME, SK, GAS, and HHS contributed to interpretation of findings. MPC, MQ, BR, FB, PB, HW, JLY, JML, TH, AM, GG, MSant, GAS, HHS, and HT drafted the report. All authors revised the report.

Conflicts of interest
The authors declared no conflicts of interest.

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ARTICLE | Annals of Internal Medicine

Declining Incidence of Hepatocellular Carcinoma in Osaka, Japan, from 1990 to 2003

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Background: Japan has the highest incidence rate of primary liver cancer attributed to chronic hepatitis C virus (HCV) infection among developed countries. Molecular clock analysis of HCV sequences revealed that the spread of HCV took place earlier in Japan than in other countries. This might influence recent temporal trends in hepatocellular carcinoma (HCC) incidence.

Objective: To characterize the contribution of HCV-related hepatocellular carcinoma (HCC) to recent changes in HCC incidence in Osaka, Japan.

Design: Population-based survey.

Setting: Osaka Cancer Registry and 10 hospitals in Osaka.

Participants: 63 862 patients with HCC that was diagnosed between 1981 and 2003 in Osaka Prefecture, including 5253 HCV-seropositive patients with HCC that was diagnosed between 1990 and 2003 at 10 hospitals.

Measurements: Incidence of HCC and estimated incidence rate of HCV-related HCC, measured by multiplying the prevalence of anti-HCV by the corresponding HCC incidence rate.

Results: Between 1981 and 2003, peak incidence of HCC among men age 50 to 59 years, 60 to 69 years, and 70 to 79 years occurred in 1986, 1995, and 2000, respectively, with marked downward trends thereafter (average annual change, −7.9, −22.3, and −12.4 per 100 000 persons, respectively). Similar trends were observed in women. Estimated sex- and age-specific incidence of HCV-related HCC (per 100 000 persons) decreased from 255 to 92 cases at the maximum in men age 60 to 69 years and from 61 to 34 cases in women age 60 to 69 years, whereas estimated incidence of non-HCV–related HCC did not change between 1990 and 2003.

Limitation: Infection was determined only by HCV seropositivity.

Conclusion: The incidence of HCC in Osaka started to decrease by 2000, mainly because of decreased HCV-related HCC.

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Primary liver cancer was the fifth most common cancer worldwide by 2000, with approximately 551 000 new cases recorded (1). In most countries, hepatocellular carcinoma (HCC) comprises 85% to 90% of primary liver cancer cases. With some exceptions, developed countries, including the United States, have been experiencing an increase in the incidence of primary liver cancer, considered to be due at least in part to increased prevalence of chronic hepatitis C virus (HCV) infection (2).

Japan has had one of the highest incidence rates of primary liver cancer among developed countries (age-standardized incidence rate in 1995, 25.5 per 100 000 men and 7.7 per 100 000 women) (3). Approximately 90% of liver cancer cases are HCC, which, in Japan, is mainly caused by chronic HCV infection rather than chronic hepatitis B virus infection (4). A recent report on the age-standardized incidence of primary liver cancer among Japanese men, which was calculated from 6 population-based cancer registries, showed a sharp increase that started in the mid-1970s but leveled off in the mid-1990s (5). These distinctive trends were thought to be due to the spread of HCV infection, which began in the 1920s and increased after World War II (6–8). Thus, HCV penetrated Japan earlier than Spain, Egypt, the United States, the former Soviet Union, South Africa, and Hong Kong, as evidenced by molecular clock analysis of the sequences of HCV isolates (8). However, recent temporal trends regarding incidence rates of HCC and the contribution of HCV infection have not been clearly documented in the Japanese population.

We analyzed temporal trends for HCC incidence rates between 1981 and 2003 in Osaka Prefecture (population in 2005, 8.8 million) and interpreted these in the context of HCV infection rates.

See also:

Print
Editors' Notes 821

Web-Only
Conversion of graphics into slides

Methods

Data Collection on Incident HCC Cases

We obtained data on incident HCC cases from the Osaka Cancer Registry, which was established by the Osaka Prefectural Government in 1962. The registry collects reports on patients with newly diagnosed cancer, including demographic and cancer-related information, from all medical institutions in Osaka Prefecture (9). These have been routinely supplemented by death certificates gathered

by the Osaka Prefectural Government (9). For patients with cancer who were enrolled in the registry on the basis of their death certificate, we contacted the issuing hospital to obtain information on diagnosis and treatment and to establish the date of HCC incidence, which we determined to be the time of diagnosis at that hospital. We site-coded the data according to the International Classification of Diseases for Oncology, Third Edition (10). We included patients with HCC (codes 8170 through 8180). The protocol was approved by the ethics committee of the Osaka Medical Center for Cancer and Cardiovascular Diseases.

From 1981 to 2003, 48 166 men and 15 696 women with HCC were documented in the Osaka Cancer Registry. We calculated the annual age-standardized incidence rates of HCC (world population as a standard population) by sex between 1981 and 2003. To characterize temporal trends for HCC, we assessed 10-year, age-specific incidence rates of HCC between 1981 and 2003 in individuals age 50 to 79 years. We studied these particular age-specific rates because most HCV-related HCC cases in the Japanese population occur between the ages of 50 and 79 years (4). We used the annual population estimates from 1981 to 2003, which were based on the average population in each sex and age category for the Osaka Prefecture during the particular period, as denominators for calculating incidence rates. The annual population estimates were based on data from the 1980, 1985, 1990, 1995, 2000, and 2005 Japanese population censuses, with linear interpolation for the years in between.

Statistical Analysis

To identify years when a statistically significant change in the slope of the temporal trend in the incidence occurred, we applied the joinpoint regression model by using the Joinpoint Regression Program, version 3.0 (U.S. National Cancer Institute, Bethesda, Maryland). We assumed constant variance and uncorrelated errors (11) because we could not detect heteroskedasticity by the White test or autocorrelation by the Durbin-Watson test in men or women in any age group.

We computed the estimated slopes describing the average annual change of incidence rate per 100 000 persons and the corresponding 95% CIs for each trend by fitting a piecewise regression line to the rates, using calendar year as a regression variable. We used the permutation test method to identify years when a statistically significant change had occurred ($P < 0.05$) and set the number of randomly permuted data sets at 4499. We set the number of joinpoints to a minimum of 0 and a maximum of 3 in the Joinpoint Regression Program.

Data Collection on Prevalence of HCV Infection among Patients with HCC

The Osaka Cancer Registry does not collect serologic data on HCV infection in the registered patients. Therefore, we used data on HCV seropositivity from patients with HCC that was diagnosed at 10 hospitals in Osaka Prefecture (1 university hospital, 2 cancer centers, and 7 general hospitals) to estimate the prevalence of HCV infection in patients with HCC. We considered the HCC diagnosis confirmed when the patient had positive histologic or positive radiologic results by enhanced computed tomography or hepatic angiography. We collected data on the patient's sex, date of birth, date of diagnosis between 1990 and 2003, first Chinese letter of the family name, and presence of hepatitis B surface antigen and antibody to hepatitis C (anti-HCV) as assessed by any commercially available kit. We did not collect the full first and family name for reasons of confidentiality. Because anti-HCV testing first became available in Japan in 1990, we collected data on patients whose HCC diagnosis was between 1990 and 2003. One investigator checked for duplication of the data set, because some patients might have been registered multiple times among the participating hospitals as a result of referrals and recurrence of HCC. We defined HCV-related HCC as occurring in patients who were HCV-seropositive at the time of diagnosis.

We calculated the sex-specific, age-specific (50 to 59, 60 to 69, or 70 to 79 years), and period-specific (1990 to 1992, 1993 to 1995, 1996 to 1998, 1999 to 2001, or 2002 to 2003) prevalences of HCV seropositivity for patients with HCC. We then multiplied prevalence rates by the corresponding strata of the HCC incidence rate obtained from the Osaka Cancer Registry data. Thus, we derived the denominators from the general population in Osaka through the denominators of the HCC incidence rate and obtained the numerators by multiplying the prevalence rates by the HCC incidence rate. We calculated the incidence rate of non–HCV-related HCC by subtracting HCV-related HCC from total HCC. Thus, we describe trends for the estimated incidence rates of HCV-related

Context

Hepatitis C virus (HCV) infection in Japan began to spread during the 1920s, increased after World War II with an explosion in parenteral amphetamine use and paid blood donation, and decreased in the 1950s to 1960s with voluntary blood donation and penalties against amphetamine use. Evidence linking the trends in HCV infection to hepatocellular carcinoma rates in Japan is limited.

Contribution

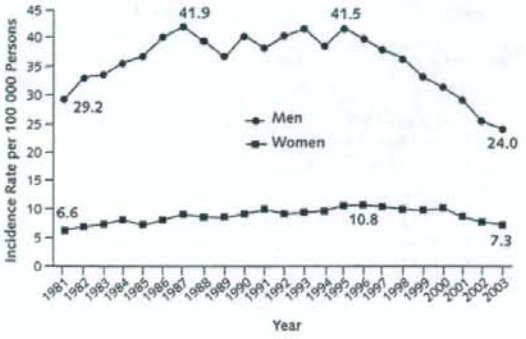
Data from the Osaka Cancer Registry and 10 Osaka hospitals suggest that hepatocellular carcinoma rates began to decrease in 2000, mainly because of a decrease in HCV-associated cancer.

Implication

Control of HCV transmission within a population seems to be followed by a decrease in hepatocellular carcinoma.

—The Editors

Figure 1. Trends in age-standardized (world population) incidence of hepatocellular carcinoma in Osaka, Japan, 1981–2003.



and non–HCV-related HCC between 1990 and 2003 in Osaka Prefecture. We calculated the CI of the estimated rates by multiplying the lower and upper limits of the CI of the prevalence based on SE by the corresponding HCC incidence rate.

Role of the Funding Source

This study was supported by the Osaka Prefectural Government between 1990 and 2000 and Grants-in-Aid for Hepatitis Research of the Japanese Ministry of Health, Labor, and Welfare. There is no conflict of interest in the study. The funding sources had no role in the collection, management, or analysis of data.

RESULTS

The age-standardized incidence rate of HCC in men increased between 1981 and 1987 from 29.2 to 41.9 cases per 100 000 persons, then fluctuated until 1995. After that, it steadily decreased to 24.0 cases per 100 000 persons in 2003 (Figure 1). Among women, the age-standardized incidence rate of HCC increased between 1981 and 1996 from 6.6 to 10.8 cases per 100 000 persons, then gradually decreased to 7.3 cases per 100 000 persons in 2003 (Figure 1).

Figure 2 shows the trends in the incidence of HCC among men and women age 50 to 59 years, 60 to 69 years, and 70 to 79 years in Osaka between 1981 and 2003. The HCC incidence rate increased from 1981 to 1986 among men age 50 to 59 years, from 1981 to 1995 among men age 60 to 69 years, and from 1981 to 2000 among men age 70 to 79 years (average annual change of the incidence rate [per 100 000 persons], 10.0, 10.7, and 6.2, respectively) (Table 1). A striking downward trend occurred after the year of peak incidence in the 3 age groups (−7.9 until 1996, −22.3 until 2003, and −12.4 until 2003, respectively). Among men age 50 to 59 years, there was a second joinpoint (a change from rapid to moderate decrease) in 1996, resulting in a slope of −3.1 until 2003. Among women age 50 to 59 years, 60 to 69 years, and 70 to 79 years, the incidence rates of HCC peaked in 1991, 1997, and 2000, respectively (Table 1). The rates in women seemed to increase slightly from 1981 until the year of the joinpoint, with slopes of 0.43, 2.07, and 3.10, respectively. Thereafter, HCC incidence rates in women decreased through 2003 at a statistically significant average annual rate of −0.9, −5.7, and −7.9, respectively (Table 1).

Figure 2. Joinpoint analysis of the incidence rate of hepatocellular carcinoma among individuals age 50 to 79 years in Osaka, Japan, 1981–2003.

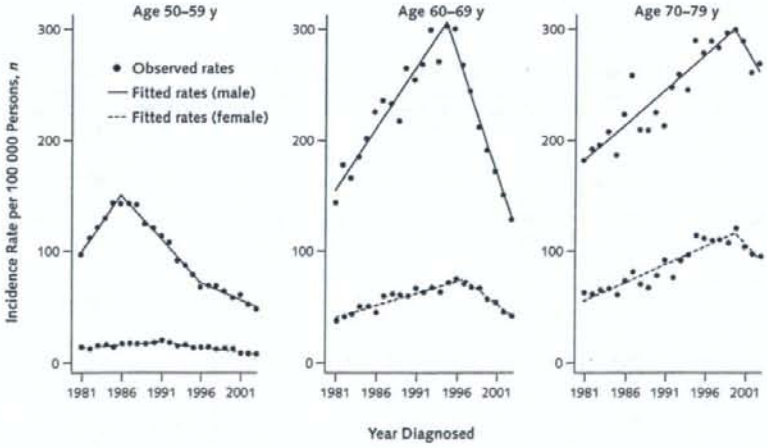


Table 1. Joinpoint Analysis of the Hepatocellular Carcinoma Incidence Rate per 100 000 Persons in Osaka, Japan, 1981–2003

Age Range	Peak Year	Incidence Rate per 100 000 Persons	Trend 1		Trend 2		Trend 3	
			Years	Slope (95% CI)	Years	Slope (95% CI)	Years	Slope (95% CI)
Men								
50–59 y	1986	142.0	1981–1986	10.0 (8.2 to 11.8)*	1986–1996	−7.9 (−8.6 to −7.1)*	1996–2003	−3.1 (−4.2 to −2.1)*
60–69 y	1995	299.6	1981–1995	10.7 (9.1 to 12.3)*	1995–2003	−22.3 (−26.0 to −18.6)*	–	–
70–79 y	2000	296.4	1981–2000	6.2 (4.8 to 7.5)*	2000–2003	−12.4 (−35.7 to 10.9)	–	–
Women								
50–59 y	1991	19.7	1981–1991	0.4 (0.2 to 0.7)*	1991–2003	−0.9 (−1.1 to −0.7)*	–	–
60–69 y	1997	68.5	1981–1997	2.1 (1.7 to 2.4)*	1997–2003	−5.7 (−7.3 to −4.1)*	–	–
70–79 y	2000	118.1	1981–2000	3.1 (2.5 to 3.7)*	2000–2003	−7.9 (−18.1 to 2.4)	–	–

* $P < 0.001$.

Table 2 shows the prevalence of anti-HCV antibodies among 5253 patients age 50 to 79 years with HCC that was diagnosed at 10 hospitals in Osaka between 1990 and 2003. The prevalence was highest in men with HCC that was diagnosed in 1993 to 1995 (82.4%). The proportion of HCV-seronegative patients ranged from 18% to 29% through the observation period. The prevalence of anti-HCV was almost constant (81% to 83%) among women with HCC that was diagnosed between 1993 and 2003 (Table 2).

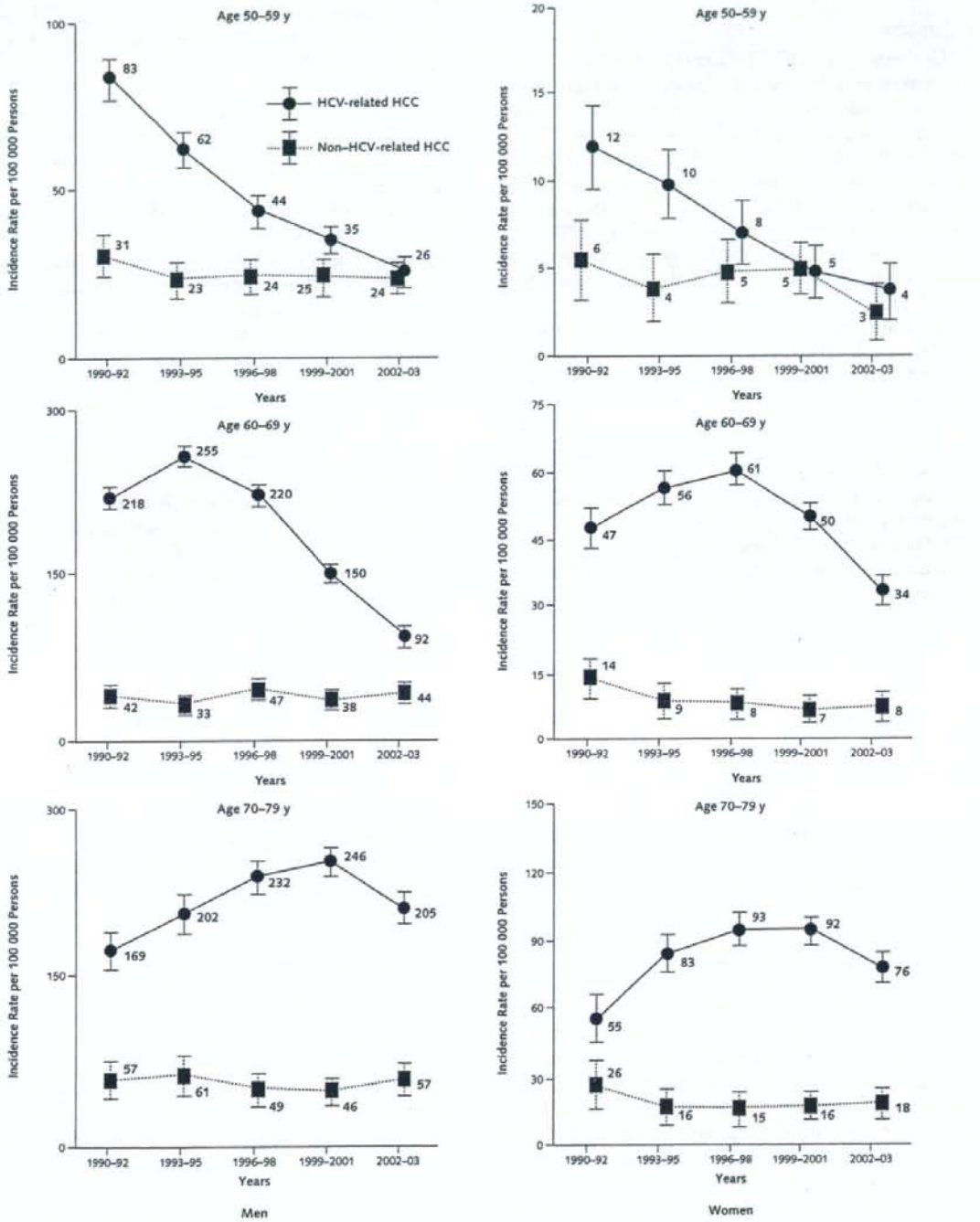
Figure 3 shows changes in the estimated incidence rate of HCV-related and non–HCV-related HCC from 1990 to 2003. Among men, the estimated incidence rate of HCV-related HCC steadily decreased among Osaka residents age 50 to 59 years from 83 (95% CI, 77 to 89) cases per 100 000 persons in 1990 to 1992 to 26 (CI, 21 to 30) cases per 100 000 persons in 2002 to 2003. Among men age 60 to 69 years, incidence seemed to peak (255 [CI, 247 to 264] cases per 100 000 persons) from 1993 to 1995. Among men age 70 to 79 years, the incidence rate increased from 1990 to 1992 (169 [CI, 153 to 186] cases per 100 000 persons) to 1999 to 2001 (246 [CI, 234 to 258] cases per 100 000 persons) and leveled off afterward. The estimated incidence rate of HCV-related HCC among women age 50 to 59 years decreased from 12.4 (CI, 10.1 to 14.7) cases per 100 000 persons during 1990 to 1992 to 4.2 (CI, 2.5 to 5.8) cases per 100 000 persons during 2002 to 2003, whereas among women age 60 to 69 years, the incidence peaked (61 [CI, 57 to 64] cases per 100 000 persons) during 1996 to 1998. The trend in women age 70 to 79 years seemed to be similar to that in men of the same age: increasing during the 1990s and leveling off in the early 2000s (Figure 3). The estimated incidence rate of non–HCV-related HCC was lower than that of HCV-

Table 2. Prevalence of Anti-HCV among 5253 Patients Age 50 to 79 Years with Hepatocellular Carcinoma at 10 Hospitals in Osaka, Japan, 1990–2003*

Variable	1990–1992		1993–1995		1996–1998		1999–2001		2002–2003	
	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %	Patients, *n*	Prevalence (±SE), %
Men										
Anti-HCV(+)	602	78.3 ± 1.5	677	82.4 ± 1.3	651	78.7 ± 1.4	709	76.6 ± 1.4	385	70.9 ± 1.9
Anti-HCV(+) and HBsAg(+)	18	2.3 ± 0.5	17	2.1 ± 0.5	11	1.3 ± 0.4	16	1.7 ± 0.4	8	1.5 ± 0.5
Anti-HCV(+) and HBsAg(−)	584	75.9 ± 1.5	660	80.3 ± 1.4	640	77.4 ± 1.5	693	74.8 ± 1.4	377	69.4 ± 2.0
Anti-HCV(−)	167	21.7 ± 1.5	145	17.6 ± 1.3	176	21.3 ± 1.4	217	23.4 ± 1.4	158	29.1 ± 1.9
Anti-HCV(−) and HBsAg(+)	60	7.8 ± 1.0	57	6.9 ± 0.9	71	8.6 ± 1.0	106	11.4 ± 1.0	68	12.5 ± 1.4
Anti-HCV(−) and HBsAg(−)	107	13.9 ± 1.2	88	10.7 ± 1.1	105	12.7 ± 1.2	111	12.0 ± 1.1	90	16.6 ± 1.6
Total	769	100.0	822	100.0	827	100.0	926	100.0	543	100.0
Women										
Anti-HCV(+)	165	73.0 ± 3.0	211	82.7 ± 2.4	248	82.9 ± 2.2	274	80.8 ± 2.1	200	81.0 ± 2.5
Anti-HCV(+) and HBsAg(+)	8	3.5 ± 1.2	2	0.8 ± 0.6	5	1.7 ± 0.7	2	0.6 ± 0.4	2	0.8 ± 0.6
Anti-HCV(+) and HBsAg(−)	157	69.5 ± 3.1	209	82.0 ± 2.4	243	81.3 ± 2.3	272	80.2 ± 2.2	198	80.2 ± 2.5
Anti-HCV(−)	61	27.0 ± 3.0	44	17.3 ± 2.4	51	17.1 ± 2.2	65	19.2 ± 2.1	47	19.0 ± 2.5
Anti-HCV(−) and HBsAg(+)	21	9.3 ± 1.9	17	6.7 ± 1.6	29	9.7 ± 1.7	29	8.6 ± 1.5	18	7.3 ± 1.7
Anti-HCV(−) and HBsAg(−)	40	17.7 ± 2.5	27	10.6 ± 1.9	22	7.4 ± 1.5	36	10.6 ± 1.7	29	11.7 ± 2.0
Total	226	100.0	255	100.0	299	100.0	339	100.0	247	100.0

* HBsAg = hepatitis B surface antigen; HCV = hepatitis C virus.

Figure 3. Trends in estimated incidence rates of hepatitis C virus (*HCV*)–related and non–HCV-related hepatocellular carcinoma (*HCC*) in Osaka, Japan, 1990–2003.



Information on anti-HCV status only became available after 1989. Error bars indicate 95% CIs.

related HCC in most strata. We observed no distinctive changes in the temporal trends for non–HCV-related HCC during the study period.

Discussion

Our analysis of HCC incidence in the Japanese population between 1981 and 2003 identified calendar years in which significant changes in temporal trends occurred. The HCC incidence rates in men and women age 50 to 59 years peaked during 1986 and 1991, respectively; in men and women age 60 to 69 years during 1995 and 1997, respectively; and in men and women age 70 to 79 years in 2000. We also found that temporal trends for HCC incidence between 1990 and 2003 by age group were mainly determined by trends in the incidence rates of HCV-related HCC.

The most likely explanation for these observations is the particular mode of HCV transmission in Japanese society. According to a study on molecular tracing of endemic HCV (8), the exponential spread of HCV-1b infection, a dominant genotype of HCV in Japan, started in the 1920s. This was associated with treatment of *Schistosoma japonicum* beginning in 1921 (12). Later, HCV infection coincided with an increase in parenteral amphetamine use in the devastated country during and after World War II (6, 7). Subsequently, viral spread was considered to be amplified through blood transfusions and parenteral medical procedures in the 1950s and 1960s (6, 7). Data on first-time blood donor candidates in Osaka indicate that the prevalence of anti-HCV antibodies among those born in 1925 to 1935 was much higher (7% to 10%) than that in the younger generation born in 1936 to 1955 (13). It is plausible that Japanese people born between 1925 and 1935, who were adolescents in the early 1950s, were most susceptible to HCV transmission under these circumstances. Age groups with peak incidence of HCC in men and women in the current study (1986 and 1991, respectively, for 50 to 59 years; 1995 and 1997, respectively, for 60 to 69 years; and 2000 for 70 to 79 years) included the generation for which prevalence of anti-HCV was high in Osaka (born in 1925 and 1935) (13). Stiffening of legal penalties against amphetamine use starting in 1954 and conversion from paid to voluntary blood donation in the late 1960s may have reduced HCV transmission, thereby resulting in the lower prevalence of HCV infection in generations born after 1935. Indeed, the spread of HCV in Japan essentially ended by the early 1990s at the latest, as evidenced by the current very low incidence of HCV infection among repeat blood donors (14, 15). Better detection methods introduced in the early 1980s for HCC in patients with cirrhosis through ultrasonography and measurement of α-fetoprotein may have contributed to the apparent increase in the incidence of HCC found in this study. However, the distinctive changes we observed in the age-specific incidence of HCC during the 1990s through the early 2000s cannot be explained by the increased ability to detect HCC, because the different joinpoints in age-specific incidence rates would not be derived from a single period effect of detection of HCC.

Increases in the incidence of and deaths from liver cancer in the 1970s to 1990s have been reported in Japan (5, 16), Australia (2), the United Kingdom (17), France (2, 18), Italy (2, 18), and the United States (2, 19). The increases in Japan and the United States are attributable to increased seroprevalence of HCV (6, 13, 20, 21), whereas this relationship has not been clearly established in the other countries.

Certain limitations of this study should be considered. First, because cancer reporting in Osaka is not mandated by law, HCC could have been underreported. However, because it is fatal, most of the unreported cases should have been detected by examination of the death certificate. In addition, because the proportion of persons with HCC included only on the basis of their death certificate was almost constant (22% to 25%) during the observation period (22–24), such underreporting would not be expected to affect the temporal trends for HCC incidence rates shown in our study. Second, the proportion of HCV-seropositive patients among the 5253 cases diagnosed at 10 hospitals might differ somewhat from the entire cohort of patients with HCC in Osaka. However, all Japanese patients, including those with HCC, have easy access to hospitals because of the national medical insurance system, and the 10 participating hospitals did not select patients with HCC on the basis of their etiologic background. Therefore, it is realistic to suppose that selection bias on prevalence of anti-HCV among these 5253 patients would have been limited. Finally, the temporal trends seen in the present study might differ from those among the entire Japanese population. We previously reported age-specific incidence rates of liver cancer by birth year in Japanese men between 1962 and 1997 (5) by using 6 population-based cancer registries from Cancer Incidence in Five Continents (9) (registries for Miyagi, Yamagata, Osaka, Hiroshima, Saga, and Nagasaki). Our previous study found the peak incidence of HCC among those born between 1931 and 1935 (5). In addition, the age-dependent prevalence of anti-HCV among first-time blood donors in Osaka (13) was similar to those in other areas of Japan (25). These findings may indicate that the timing of the outbreak of HCV infection and its reduction were similar in the different geographic areas of the country.

In conclusion, our calculation of HCC incidence rates demonstrated that they are already decreasing in both sexes in Osaka, Japan. That the outbreak of HCV infection in Japan after World War II and its termination occurred earlier in Japan than in the rest of the world is the most likely explanation for these observations. These findings confirm that HCV-related HCC is a preventable disease that can be decreased by controlling parenteral HCV transmission. In the early 1990s, interferon therapy for patients

with chronic HCV infection was started in Japan to reduce the risk for HCC (26, 27). A nationwide, community-based anti-HCV screening system targeting individuals age 40 to 70 years was introduced by municipal governments in Japan in 2002. Further observation of the temporal trends of HCC incidence is needed to assess the efficacy of these interventions in Japan.

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Trends in Lung Cancer Incidence by Histological Type in Osaka, Japan

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Background: In Japan, an increase in age-adjusted incidence rates of lung adenocarcinoma (ADC) and a decrease in lung squamous cell carcinoma (SQCC) have been reported.
Methods: The number of lung cancer incidence, age-adjusted rates, and age-specific rates by birth-cohort according to histological type were examined using the data from Osaka Cancer Registry.
Results: The numbers of lung cancer incidence among men and women have increased, particularly in ADC. The age-adjusted incidence rates of ADC among men and women have continuously increased, while those of SQCC and small cell carcinoma (SMCC) turned to decrease since 1990s. A trough of lung cancer incidence rates was observed among men in 1935–39 birth-cohorts. The declining trend appeared in 1955–59 birth-cohorts. Lung cancer incidence rates among women have increased since 1895–99 birth-cohorts, but those rates leveled off or decreased in 1950s birth-cohorts. Trends of ADC by birth-cohort were almost the same as those of all histological types. The SQCC among men peaked in 1915–19 birth-cohorts, and decreased in the subsequent birth-cohorts. The SMCC among men peaked in 1920s birth-cohorts, and decreased or leveled off in the subsequent birth-cohorts.
Conclusions: Lung cancer incidence rates by birth-cohorts were almost parallel to the smoking prevalence. However, those for ADC among young women in 1950s birth-cohorts were not parallel to the smoking prevalence, which requires careful monitoring to confirm such findings.

Key words: lung cancer – incidence – histological type – birth-cohort

BACKGROUND

Lung cancer is the leading cause of cancer deaths in Japan, with 45 927 men and 17 307 women dying from lung cancer in 2006. To date, increase in the incidence rates of lung adenocarcinoma (ADC) and decrease in the incidence rates of squamous cell carcinoma (SQCC) and small cell carcinoma (SMCC) have been reported in Japan (1,2). The same trend has been reported in Western countries also (3–5). Some previous studies reported that there was a trough of lung cancer incidence or mortality in Japanese male 1935–39 birth-cohorts because of the limited cigarette supply just after World War II (6–10). Soda et al. (7) reported the birth-cohort analysis by histological type using Nagasaki Cancer Registry in 2000. However, this study was based on the small number of registered lung cancer cases and excluded the cases without histological diagnoses.

In the present study, we updated the recent trends in lung cancer incidence by histological type and tried to clarify their characteristics by birth-cohort, using the data from Osaka Cancer Registry (OCR) with the large number of lung cancer incidence.

MATERIALS AND METHODS

OCR, which started in 1962, is the population-based cancer registry covering Osaka prefecture (population: 8.8 million, 2005 census). Using OCR data on lung cancer incidence

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(International Classification of Diseases 10th revision C33–C34) diagnosed between 1975 and 2003, we calculated the number of lung cancer incidence per year, age-adjusted rates and age-specific rates by birth-cohort according to histological type.

Histological types were categorized into three major types: ADC (ICD-O: 8140, 8141, 8200, 8211, 8250, 8251, 8260, 8310, 8323, 8440, 8470, 8480, 8481 and 8490), SQCC (ICD-O: 8050, 8052 and 8070–8076), SMCC (ICD-O: 8041–8045) and the others.

Incident years are divided into 5-year periods: 1975–78, 1979–83, 1989–93, 1994–98 and 1999–2003. Birth years were also divided into 5-year periods. The population data by age group in Osaka prefecture were obtained from the data of Population Census. For age-standardization, the Japanese model population in 1985 was used.

The data from OCR included the cases without specific histological diagnosis: a maximum of 60.4% in 1975–78 and a minimum of 31.4% in 1994–98. Based on the assumption that distributions of histological types in the same sex and age group were the same between those with and without a specific histological type, we compensated for the proportion of cases without a specific histological type. The detailed procedure was followed to the previous study (1); first, the sex-, age (5-year)- and incident year (or birth-cohort)-specific numbers of incidence were calculated for all histological types including the cases without histological diagnosis. Second, the sex-, age (10-year)- and incident year (or birth-cohort)-specific proportion of each histological type among the cases with histological diagnosis were calculated for three major histological types. Finally, the sex-, age (5-year)-, incident year (or birth-cohort)-specific number of incidence were multiplied by the corresponding sex-, age- and incident year (or birth-cohort)-specific proportion to approximate the number of incidence by histological type.

RESULTS

Table 1 shows the trends in the number of lung cancer incidence per year according to histological type. Lung cancer incidence per year for all histological types among men and women increased consistently; from 1086 in 1975–78 to 3487 in 1999–2003 among men and from 395 in 1975–78 to 1482 in 1999–2003 among women. As for histological type, the number of ADC incidence has increased remarkably among men and women. The shift in main histological type among men occurred in the 1990s.

Table 2 shows the trends in the age-adjusted rates according to the histological type. The age-adjusted rates for all histological types peaked in 1994–98 and recently leveled off among men, while those consistently increased among women. The rates for ADC consistently increased among men and women. In contrast, the rates for SQCC and SMCC peaked in 1989–93 among men, and decreased subsequently. Those rates for SQCC and SMCC peaked in 1984–88 and 1989–93, respectively, among women, and decreased subsequently.

Fig. 1 shows the trends in the age-specific lung cancer incidence rates with 95% confidence interval by birth-cohort for all histological types. Among men, there was a trough in rates for all age groups in 1935–39 birth-cohorts, which was consistent with the previous findings (7,10). In the subsequent birth-cohorts, the rates increased for all age groups, but the declining tendency appeared in 1955–59 birth-cohorts. Among women, the trough in rates in 1935–39 birth-cohorts was not confirmed. The rates for aged $\geq$50 years increased gradually, while it seemed that the rates for aged <50 years turned to decrease or level off after 1950–54 birth-cohorts: however, these trends were unstable because of the wide confidence intervals due to the small number of incidence.

Table 1. Trends in the number of lung cancer incidence per year according to histological type

Histological type	Incident year					
	1975–78	1979–83	1984–88	1989–93	1994–98	1999–2003
Men						
Adenocarcinoma (%)	372 (34.2)	510 (35.7)	696 (35.5)	853 (35.8)	1191 (40.2)	1497 (42.9)
Squamous cell carcinoma (%)	474 (43.6)	582 (40.8)	760 (38.8)	921 (38.6)	1086 (36.6)	1208 (34.7)
Small cell carcinoma (%)	142 (13.0)	203 (14.2)	315 (16.1)	410 (17.2)	483 (16.3)	543 (15.6)
Others (%)	99 (9.1)	132 (9.3)	189 (9.7)	200 (8.4)	204 (6.9)	239 (6.8)
All histological types (%)	1086 (100)	1428 (100)	1961 (100)	2383 (100)	2964 (100)	3487 (100)
Women						
Adenocarcinoma (%)	242 (61.2)	328 (60.2)	453 (58.7)	579 (60.3)	792 (64.8)	996 (67.2)
Squamous cell carcinoma (%)	86 (21.9)	106 (19.5)	163 (21.2)	184 (19.2)	218 (17.9)	241 (16.3)
Small cell carcinoma (%)	32 (8.0)	73 (13.3)	97 (12.5)	132 (13.7)	152 (12.5)	178 (12.0)
Others (%)	35 (8.9)	38 (6.9)	59 (7.6)	65 (6.8)	60 (4.9)	66 (4.4)
All histological types (%)	395 (100)	545 (100)	772 (100)	961 (100)	1223 (100)	1482 (100)