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Survival following early-stage colon cancer: an ACCENT-based comparison of patients versus a matched international general population†

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Background: Post-treatment survival experience of early colon cancer (CC) patients is well described in the literature, which states that cure is probable for some patients. However, comparisons of treated patients' survival versus that expected from a matched general population (MGP) are limited.

Patients and methods: A total of 32 745 patients from 25 randomized adjuvant trials conducted from 1977 to 2012 in 41 countries were pooled. Observed long-term survival of these patients was compared with expected survival matched on sex, age, country, and year, both overall and by stage (II and III), sex, treatment [surgery, 5-fluorouracil (5-FU), 5-FU + oxaliplatin], age (<70 and 70+), enrollment year (pre/post 2000), and recurrence (yes/no). Comparisons were made at randomization and repeated conditional on survival to 1, 2, 3, and 5 years. CC and MGP equivalence was tested, and observed Kaplan–Meier survival rates compared with expected MGP rates 3 years out from each landmark. Analyses were also repeated in patients without recurrence.

Results: Within most cohorts, long-term survival of CC patients remained statistically worse than the MGP, though conditional survival generally improved over time. Among those surviving 5 years, stage II, oxaliplatin-treated, elderly, and recurrence-free patients achieved subsequent 3-year survival rates within 5% of the MGP, with recurrence-free patients achieving equivalence.

Conclusions: Conditional on survival to 5 years, long-term survival of most CC patients on clinical trials remains modestly poorer than an MGP, but achieves MGP levels in some subgroups. These findings emphasize the need for access to quality care and improved treatment and follow-up strategies.

Key words: early-stage colon cancer, population, meta-analysis, individual patient data, oxaliplatin chemotherapy, long-term survival

introduction

Colon cancer (CC) is a leading cause of cancer-related death, ranking third for both men and women [1] in the USA. In patients with stage III CC, the benefit of adjuvant chemotherapy following curative resection has been well established, with the definitive trials for FOLFOX [5-fluorouracil (5-FU), leucovorin, and oxaliplatin] completed roughly one decade ago [2, 3]. The survival outlook of patients with early-stage CC patients has also improved over time due to improved diagnostics [4], and in a pooled analysis of patient-level data, it was demonstrated that cure is probable in a subset of patients with early-stage CC [5]. However, to date, comparisons of the post-treatment survival experience of early-stage CC patients versus expected survival from a matched general population (MGP) have been limited,

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and the timing at which a patient might reasonably be expected to achieve an equivalent survival outlook to an otherwise similar non-cancer patient remains a challenging question.

existing population studies in colon cancer

Existing population-based studies in CC are mostly limited to comparisons between subpopulations of patients with cancer. For example, Jensen et al. [6] compared survival after colorectal cancer among Danish patients with and without ulcerative colitis. A similar population-based comparison of colorectal survival by patient sex was conducted, but limited to patients in Germany [7]. On a larger scale, Gatta et al. [8] compared colorectal cancer survival between European and US populations according to disease subsite and tumor histology, whereas Allemani et al. [9] attempted to explain persistent survival differences between Europe and US populations by accounting for stage of disease at diagnosis and adherence to treatment guidelines. Grouping data on 5489 patients collected from several population-based data resources, Sanoff et al. [10] investigated the effect of adjuvant chemotherapy on survival of stage III CC patients diagnosed at age 75 or later, finding results consistent with published trials. Focusing on conditional survival, Chang et al. [11] created a web-based tool that predicts subsequent survival of CC patients given survival to specific thresholds after initial treatment. A similar study was carried out by Zamboni et al. [12], where conditional survival and disease-free survival, were reported for subsets of patients from NSABP trials who survived without recurrence up to 5 years post-treatment. None of these recent population-based and trial-based explorations attempted, however, to compare the post-treatment survival experience of CC patients against otherwise similar patients from the general population. As a result, the question of when the long-term survival of CC patients can be expected to return to 'normal', i.e. to a level consistent with individuals who did not have CC, remains largely unanswered.

patients and methods

database

The Adjuvant Colon Cancer Endpoints (ACCENT) database contains patient-level information on more than 30 000 patients enrolled to 25 phase III adjuvant CC trials since 1977 [13, 14] (supplementary Table S1, available at *Annals of Oncology* online). Using these data, we compared the post-treatment survival of CC patients against the expected survival of the general population, where the general population was matched to ACCENT patients on age, sex, calendar year of evaluation, and country of enrollment. ACCENT patients with missing data on any matching characteristics were excluded from these analyses as their expected survival could not be reconstructed for comparison. Patients receiving adjuvant irinotecan were additionally excluded. Survival, defined as the time from randomization to death due to any cause, was right-censored at the earlier of loss of follow-up or 8 years. Recurrence times were also recorded and used to subset the ACCENT data to those patients who were recurrence-free at post-randomization analysis time points.

construction of matched general population quantities

For every patient in the ACCENT database, *expected* long-term survival based on the general population (matched on age at diagnosis, sex, country of enrollment, and year of enrollment/evaluation) was derived from life tables using the methods of Finkelstein et al. [15]. Validated life tables associated with specific countries and years were obtained from the Human Mortality Database (HMD) or World Health Organization (WHO) for this analysis [16, 17], where one such table gives the probability that an individual of a specific sex and age (in years) will survive 1 year (HMD) or 5 years (WHO). HMD tables were used for all countries when available, and where WHO survival tables were used, 1-year incremental probabilities were derived by assuming a constant risk of death across the 5-year interval. While age (in years) at randomization was uniformly collected for all ACCENT trials, exact dates of birth were not uniformly available; as such, the date and month of birth for each patient was assumed to be equal to the randomization date for the purpose of referencing life tables.

statistical comparisons

After construction of the ACCENT-matched expected population survival, long-term comparisons were carried out. First, using randomization date as the time origin, overall survival (OS) was compared overall between ACCENT patients and the MGP using a one-sample log-rank test and Kaplan–Meier analysis tailored for comparisons of a sample against a matched population constructed from life tables [15]. Specifically, the standardized mortality ratio (SMR; ratio of observed-to-expected number of deaths during follow-up) and associated 95% CI were computed, where intervals excluding SMR = 1 indicated statistically significant differences. Separately, a Kaplan–Meier survival curve with a 95% pointwise confidence band for the ACCENT patients was superimposed on the (smooth) expected survival curve based on the ACCENT–MGP. Of particular interest were the observed (ACCENT) minus expected (matched population) 3-year overall survival rates; these differences were computed and reported with 95% confidence intervals.

To investigate *conditional* survival over time of CC patients versus the general population, the analyses described above were repeated 1, 2, 3, and 5 years post-randomization, with ACCENT patients not surviving to each landmark excluded and expected survival reconstructed using the new reference time and relevant ACCENT subset.

All analyses were further carried out both overall and within groups defined by stage of disease (II and III), sex, age (< 70 and 70+), year of enrollment (pre/post 1 January 2000), grouped treatment (surgery alone, surgery + 5-FU, and surgery + FOLFOX), and recurrence before analysis time (yes and no). As disease recurrence is a time-dependent event of particular interest, results are also presented overall and within the patient subgroups after subsetting to those patients alive *and recurrence-free* at post-randomization analysis times.

results

A total of 32 745 patients from 25 randomized ACCENT trials conducted in 41 countries had complete data available for analysis (supplementary Table S2, available at *Annals of Oncology* online), whereas 12 patients were excluded for missing data. Differences in 3-year OS between ACCENT cohorts and MGPs are presented across conditional survival time points in Table 1, both overall and by subgroups of interest. The same quantities, but subsetted to patients who survived *without recurrence* to each time point, are presented in Table 2. Corresponding overall and subgroup-specific Kaplan–Meier graphs showing up to 8 years of follow-up are presented in Figures 1–3, with baseline time points of randomization, conditional survival to 5 years, and conditional survival to 5 years without recurrence, respectively. SMRs are reported for all time points and patient subgroups in supplementary Table S3 (overall) and

Table 1. Observed Kaplan–Meier survival rate minus expected (population-matched) survival rate and 95% CI for the difference, expressed as absolute percentages (%)

Cohort	*N*	Randomized (*N* = 32 745)	Lived 1 year (*N* = 31 122)	Lived 2 years (*N* = 28 421)	Lived 3 years (*N* = 25 974)	Lived 5 years (*N* = 21 949)
Overall	32 745	−14.1 (−14.6, −13.7)	−15.8 (−16.3, −15.4)	−13.5 (−13.9, −13.0)	−10.0 (−10.5, −9.6)	−5.2 (−5.7, −4.8)
Stage II	9668	**−4.8 (−5.54, −4.2)**	−6.1 (−6.7, −5.5)	−5.9 (−6.5, −5.2)	**−4.9 (−5.6, −4.2)**	**−2.8 (−3.5, −0.2)**
Stage III	23 077	−18.0 (−18.6, −17.5)	−20.1 (−20.6, −19.5)	−16.9 (−17.5, −16.4)	−12.5 (−13.1, −11.9)	−6.6 (−7.2, −5.9)
Males	17 867	−13.3 (−13.8, −12.7)	−15.5 (−16.1, −14.9)	−13.4 (−14.0, −12.8)	−10.1 (−10.7, −9.4)	−5.2 (−5.9, −4.5)
Females	14 878	−15.2 (−15.8, −14.6)	−16.3 (−16.9, −15.6)	−13.5 (−14.2, 12.9)	−10.0 (−10.6, −9.3)	−5.3 (−5.9, −4.6)
Surgery	2326	−18.6 (−20.3, −16.8)	−21.1 (−22.9, −19.2)	−18.3 (−20.2, −16.3)	−13.6 (−15.5, −11.6)	−7.1 (−9.1, −4.9)
5-FU	27 150	−14.4 (−14.9, −13.9)	−16.1 (−16.6, −15.6)	−13.7 (−14.2, −13.2)	−10.2 (−10.7, −9.7)	−5.2 (−5.7, −4.7)
Oxaliplatin	3269	−8.6 (−9.8, −7.5)	−10.2 (−11.5, −9.0)	−8.4 (−9.6, −7.2)	−6.5 (−7.7, −5.3)	**−4.5 (−6.3, −2.7)**
Age <70	26 700	−14.5 (−15.0, −14.1)	−16.6 (−17.1, −16.1)	−14.1 (−14.6, −13.6)	−10.7 (−11.2, −10.2)	−5.7 (−6.2, −5.2)
Age 70+	6045	−12.4 (−13.5, −11.3)	−12.5 (−13.6, −11.4)	−10.3 (−11.5, −9.1)	−6.7 (−7.9, −5.5)	**−3.1 (−4.5, −1.6)**
Pre-2000[a]	5667	−15.6 (−16.1, −15.0)	−17.5 (−18.1, −17.0)	−15.1 (−15.7, −14.5)	−11.3 (−11.9, −10.7)	−5.3 (−6.0, −4.6)
2000+[a]	27 078	−10.4 (−11.2, −9.7)	−12.6 (−13.3, −11.9)	−10.9 (−11.6, −10.2)	−8.4 (−9.1, −7.8)	−5.1 (−5.8, −4.3)
Recurred	(varies)	–	−77.8 (−79.2, −76.3)	−69.0 (−70.3, −67.5)	−61.5 (−63.0, −59.9)	−46.1 (−48.4, −43.7)
No recur	(varies)	–	−10.1 (−10.5, −9.7)	**−4.7 (−5.1, −4.3)**	**−1.8 (−2.2, −1.5)**	**−0.2 (−0.6, 0.2)**

Estimates are computed 3 years post-randomization and 3 years following conditional survival to years 1, 2, 3, and 5 post-randomization. Patients who received irinotecan and stage I patients were excluded from all analyses. Entries in bold indicate survival differences from the general population of <5%. Shaded cells indicate statistical equivalence between colon cancer patients and the matched general population.

[a]Patients randomized before or after 2000, respectively (grouping fixed over time).

Table 2. Patients without recurrence

Cohort	*N*	Randomized (*N* = 32 745)	AWR at 1 year (*N* = 28 299)	AWR at 2 years (*N* = 24 314)	AWR at 3 years (*N* = 22 031)	AWR at 5 years (*N* = 18 464)
Overall	32 745	−14.1 (−14.6, −13.7)	−10.1 (−10.5, −9.7)	**−4.7 (−5.1, −4.3)**	**−1.8 (−2.2, −1.5)**	**−0.2 (−0.6, 0.2)**
Stage II	9668	**−4.8 (−5.5, −4.2)**	**−3.7 (−4.2, −3.1)**	**−1.6 (−2.2, −1.1)**	**−0.7 (−1.2, −0.1)**	**0.2 (−0.4, 0.9)**
Stage III	23 077	−18.0 (−18.6, −17.5)	−13.1 (−13.6, −12.5)	−6.3 (−6.8, −5.8)	**−2.5 (−2.9, −2.0)**	**−0.5 (−1.0, 0.0)**
Males	17 867	−13.3 (−13.8, −12.7)	−10.2 (−10.7, −9.6)	**−4.8 (−5.3, −4.2)**	**−1.7 (−2.3, −1.2)**	**−0.2 (−0.8, 0.4)**
Females	14 878	−15.2 (−15.8, −14.6)	−10.0 (−10.6, −9.4)	**−4.7 (−5.2, −4.1)**	**−1.9 (−2.4, −1.5)**	**−0.2 (−0.7, 0.3)**
Surgery	2326	−18.6 (−20.3, −16.8)	−12.4 (−14.1, −10.6)	−7.1 (−8.9, −5.4)	**−4.1 (−5.8, −2.4)**	**−1.6 (−3.5, 0.3)**
5-FU	27 150	−14.4 (−14.9, −13.9)	−10.5 (−10.9, −10.0)	**−4.9 (−5.3, −4.5)**	**−2.0 (−2.4, −1.6)**	**−0.1 (−0.6, 0.3)**
Oxaliplatin	3269	−8.6 (−9.8, −7.5)	−5.7 (−6.8, −4.6)	**−1.9 (−2.8, −0.9)**	**0.4 (−0.4, 1.3)**	**−0.1 (−1.7, 1.5)**
Age <70	26 700	−14.5 (−15.0, −14.1)	−10.7 (−11.1, −10.2)	−5.2 (−5.6, −4.8)	**−2.4 (−2.8, −2.0)**	**−0.5 (−0.9, 0.0)**
Age 70+	6045	−12.4 (−13.5, −11.3)	−7.4 (−8.5, −6.4)	**−2.4 (−3.5, −1.3)**	**0.8 (−0.2, 1.9)**	**1.0 (−0.4, 2.4)**
Pre-2000[a]	5667	−15.6 (−16.1, −15.0)	−11.9 (−12.5, −11.4)	−6.4 (−6.9, −5.9)	**−3.2 (−3.7, −2.7)**	**−0.3 (−0.9, 0.3)**
2000+[a]	27 078	−10.4 (−11.2, −9.7)	−6.6 (−7.2, −6.0)	**−2.1 (−2.6, −1.6)**	**−0.1 (−0.6, 0.4)**	**0.1 (−0.6, 0.7)**

Observed Kaplan–Meier survival rate minus expected (population-matched) survival rate and 95% CI for the difference, expressed as absolute percentages (%). Estimates are computed 3 years post-randomization and 3 years following conditional survival to years 1, 2, 3, and 5 post-randomization *without recurrence*. Patients who received irinotecan and stage I patients were excluded from all analyses. Entries in bold indicate survival differences from the general population of <5%. Shaded cells indicate statistical equivalence between colon cancer patients and the matched general population.

[a]Patients randomized before or after 2000, respectively (fixed over time).

AWR, alive without recurrence.

supplementary Table S4 (recurrence-free only), available at *Annals of Oncology* online. In cases where the 95% CI for the SMR does not include 1.0, the null hypothesis of equivalent CC and population survival is rejected at the alpha = 0.05 level (*P*-values not shown).

From Table 1 and corresponding Figures 1 and 2, we find that 3-year survival probabilities for patients with CC do not return to levels within 5% of a matched population, either overall or within most patient subgroups, until patients have survived to 5 years post-randomization. Overall, at the time of initial surgery

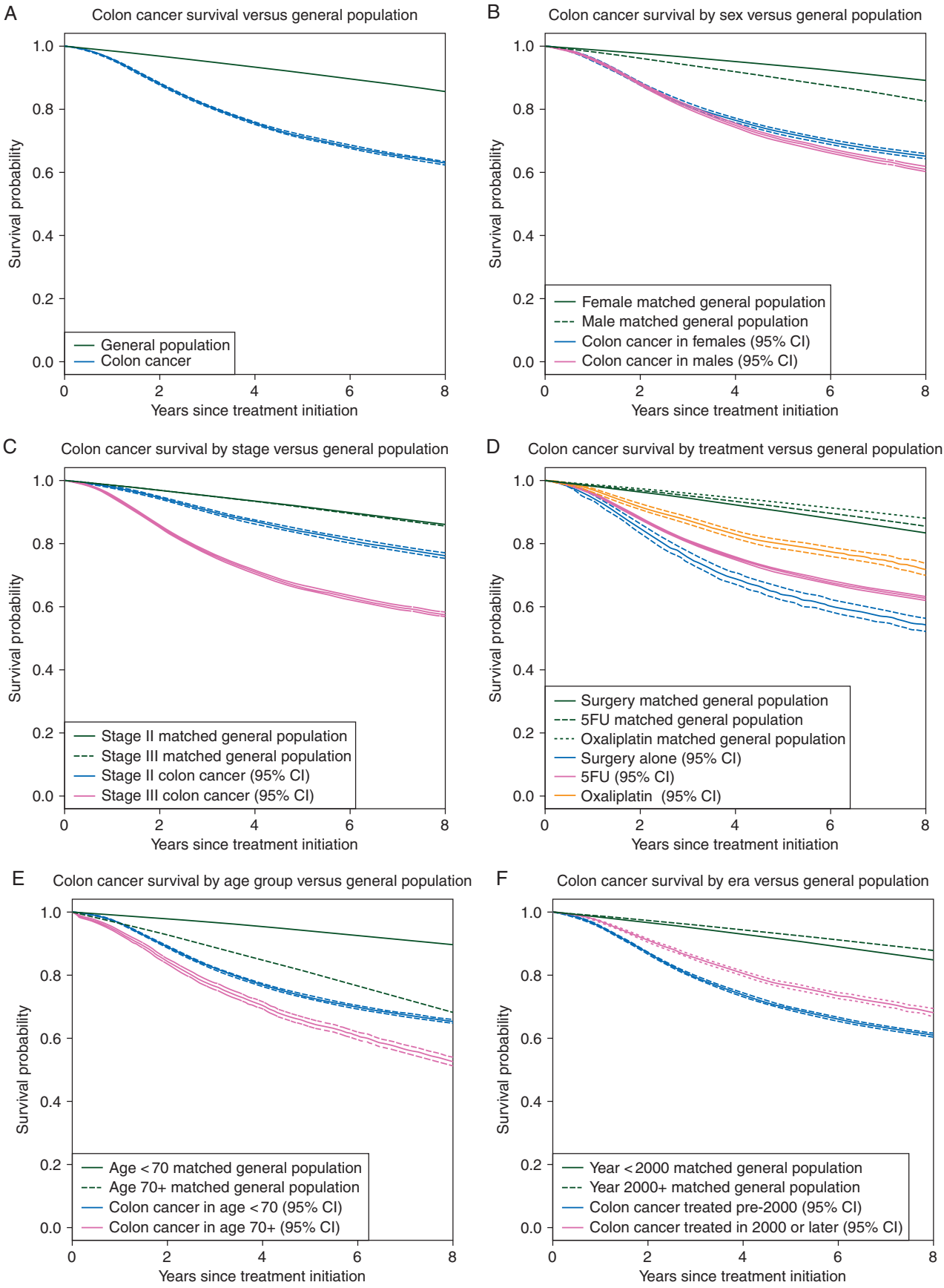

Figure 1. Kaplan–Meier survival curves for ACCENT patients *from randomization* with 95% pointwise CI, superimposed on matched population survival curves, (A) overall and by (B) sex, (C) stage of disease, (D) treatment, (E) age group, and (F) enrollment year.

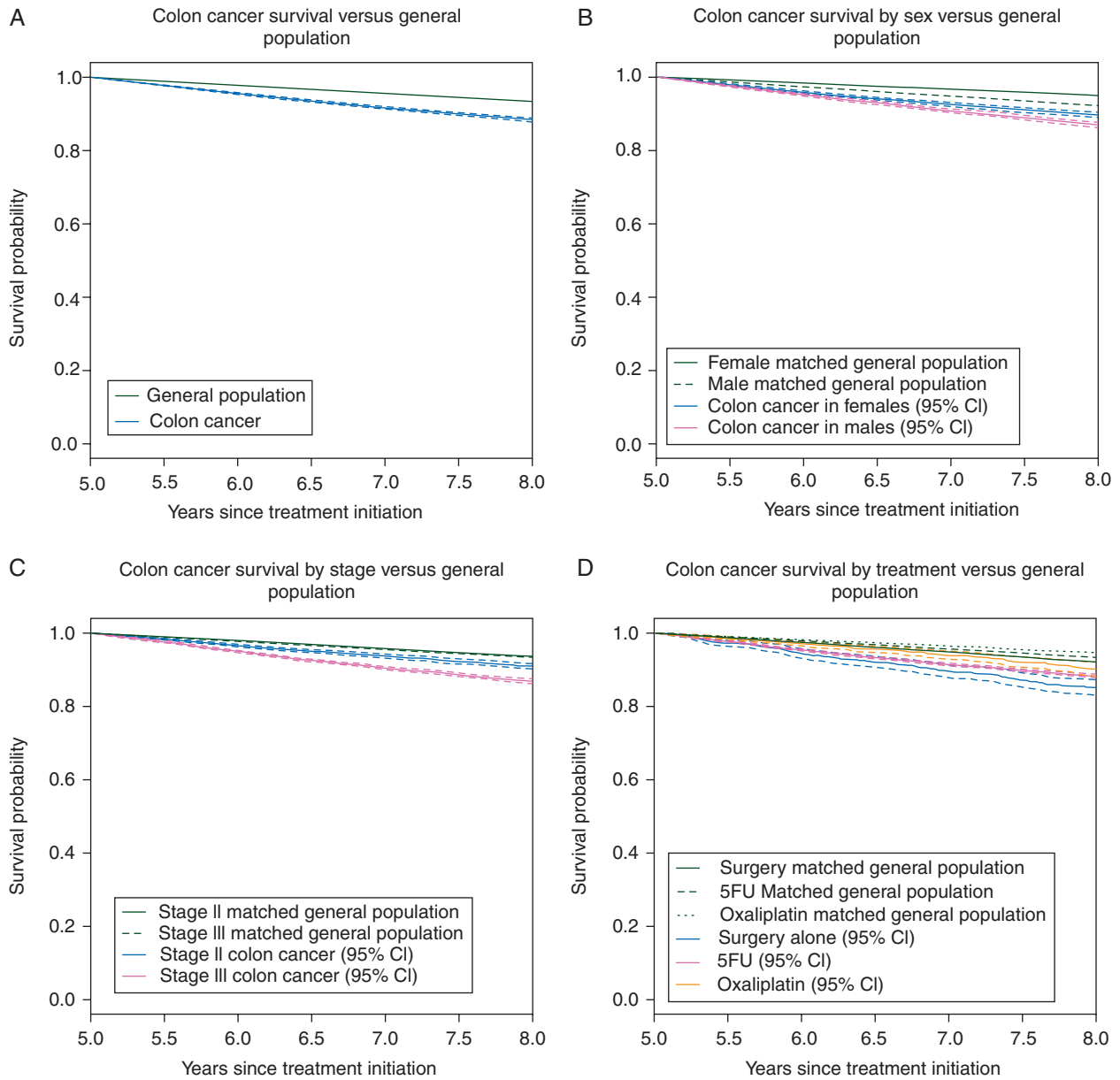

Figure 2. Kaplan–Meier survival curves for ACCENT patients with 95% pointwise CI, superimposed on matched population survival curves, (A) overall and by (B) sex, (C) stage of disease, (D) treatment, (E) age group, (F) enrollment year, and (G) recurrence, *conditional on survival to 5 years*.

or adjuvant treatment, the 3-year survival rate of all patients with early-stage (II and III) CC is 14.1% less than the MGP, with subsequent 3-year survival improving to only 5.2% less than the general population given survival to 5 years. Patients who survive without recurrence to 2 years, however, show subsequent 3-year survival only 4.7% less than the MGP. Those who additionally survive without recurrence to 5 years eventually achieve subsequent 3-year survival rates that are statistically comparable to the general population, as indicated by the expected general population rate falling within the 95% interval for the CC patient rate and an SMR statistically indistinguishable from 1.0. Another cohort with improved outcomes are patients with stage II disease, whose 3-year survival rate is only 4.8% less than the general population immediately following treatment, and only 2.8% less than the general population given survival to 5 years. As expected, the difference in 3-year survival between ACCENT patients and the MGP varies according to treatment received, with oxaliplatin-treated patients showing the best long-term outcomes, achieving subsequent 3-year survival only 4.5% less than the general population given survival to 5 years. At the same time point, patients treated with adjuvant 5-FU and those receiving surgery only have 3-year survival rates of 5.2% and 7.1% less than the general population, respectively. The difference in 3-year survival rate between patients with CC and the MGP is worse at the time of initial treatment of females than for males, but this difference becomes negligible conditional on survival to later years. The difference in 3-year survival rate between patients with CC and the general population is slightly worse for individuals <70 versus >70 years of age, and remains consistently so over subsequent conditional survival

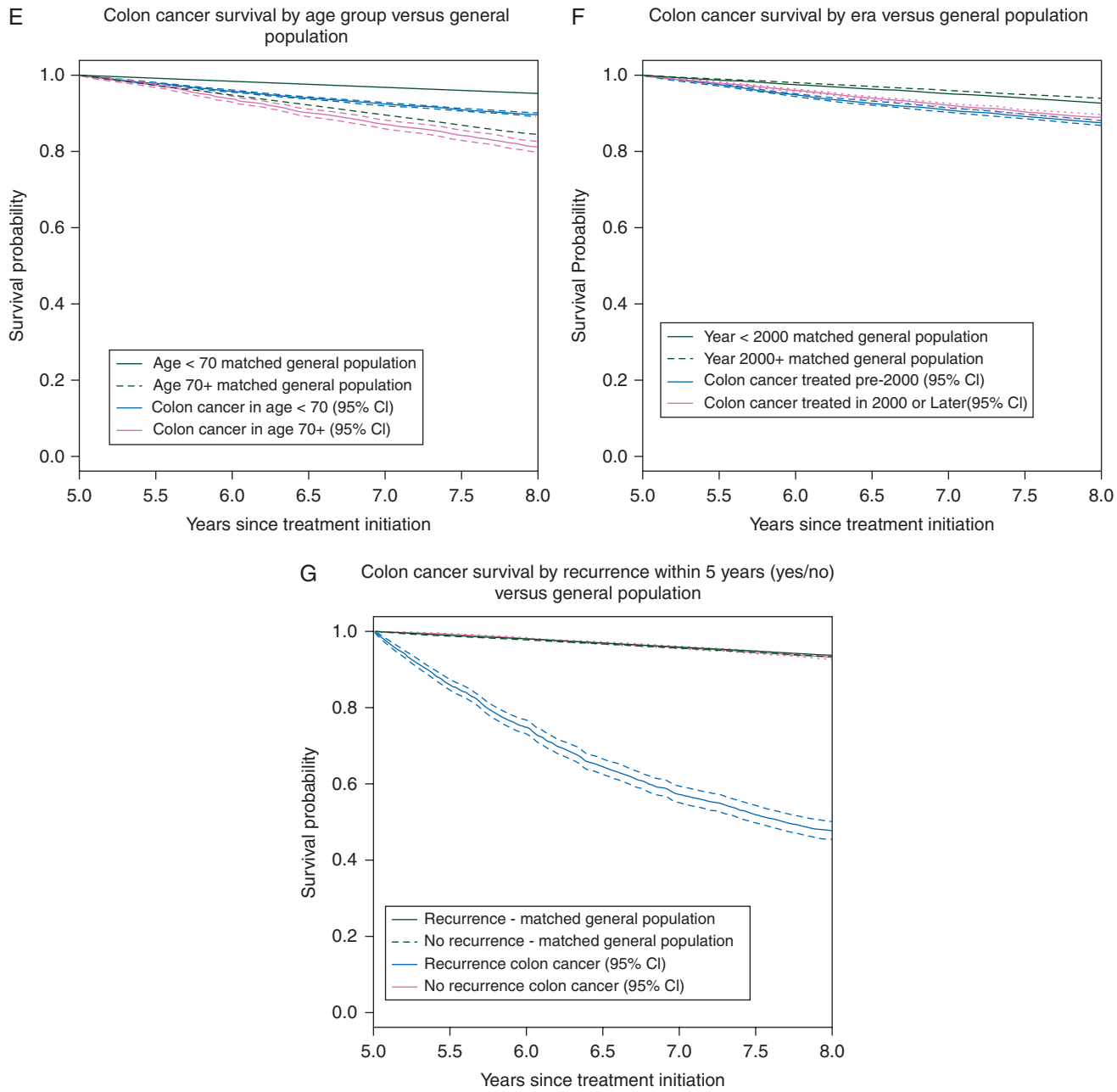

Fig. 2 *Continued*

time points. Patients initiating treatment after 2000 show smaller differences in 3-year survival rate relative to the general population across all time points, compared with patients who were treated before 2000. Those patients who survive to 2, 3, and 5 years post-randomization but are known to have had a recurrence demonstrate large differences in 3-year survival rate relative to the general population, ranging from a 77.8% decrease in subsequent 3-year survival at 1 year to a 46.1% decrease in subsequent 3-year survival at 5 years.

Overall, incidence or absence of disease recurrence is the strongest factor predicting the ACCENT patients' subsequent survival experience as well as differences from the general population. Patients who remain alive and recurrence-free show a high likelihood of achieving an expected long-term survival similar to that of the general population as they reach additional year landmarks, with statistical equivalence of subsequent 3-year survival achieved at 5 years post-treatment without recurrence (overall and for all subgroups). This equivalence is reached even sooner (by 3 years) for patients who are treated with adjuvant oxaliplatin, patients who are 70 years of age or older, and those who were treated after the year 2000.

discussion

CC remains a leading cause of cancer-related death, despite therapeutic advances. However, the survival experience of early-stage CC patients has improved in recent years, with cure possible for many patients. In this study, we addressed the questions of

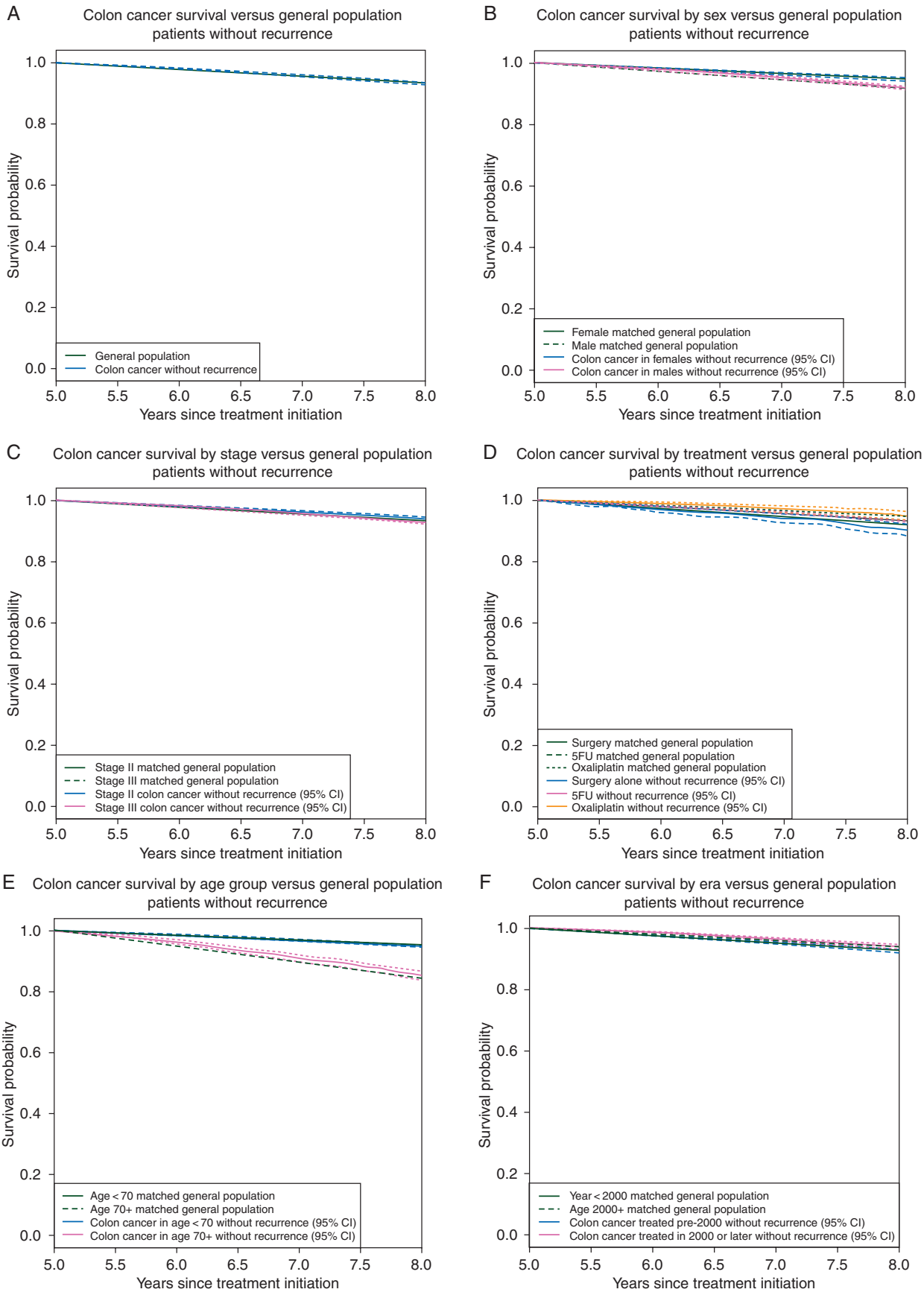

Figure 3. Kaplan–Meier survival curves for ACCENT patients *without recurrence* with 95% pointwise CI, superimposed on matched population survival curves, (A) overall and by (B) sex, (C) stage of disease, (D) treatment, (E) age group, and (F) enrollment year, *conditional on survival to 5 years*.

when and under what conditions the post-treatment survival of early-stage CC patients can reasonably be expected to resemble that of a cohort of similar individuals from the same country, age, and year in time. These results may also shed light on the expected prognoses of individual patients as they survive to annual landmarks.

As expected, we found that disease recurrence plays the strongest role in determining subsequent survival experiences relative to the general population, while stage of disease and treatment also factor strongly. While differences in conditional survival between ACCENT and matched cohorts generally lessen over time beyond the 1-year landmark, there is a subtle increase in the difference between CC and population survival that occurs from randomization to year 1 (Table 1), perhaps reflecting that the first 1–2 years post-treatment is the time of highest risk of recurrence. Also of note is the strong separation of risk differences evident for patients younger than 70 versus those 70 or older, with patients younger than 70 experiencing greater differences in survival compared with the general population, relative to elderly patients. Two factors are likely at play here on opposite ends of the age spectrum: delayed diagnosis in young CC patients having a detrimental impact on survival [18], and an increased likelihood for all causes of death among elderly patients from both the ACCENT and general populations. In fact, elderly patients who survive without recurrence to 5 years post-treatment exhibit statistically greater subsequent survival relative to their MGP (supplementary Table S4, available at *Annals of Oncology* online), reflecting the likelihood that elderly patients who are eligible for trials may be otherwise healthier or fitter than their counterparts from the general population.

One recognized limitation of this study is restriction of consideration to CC patients who were sufficiently healthy to be eligible for inclusion in clinical trials. Trial patients generally have less comorbidity than non-trial patients with the same disease, affecting generalizability of our prognostic conclusions to the broader disease population. However, these findings could remain clinically useful as a reference point when discussing prognosis with CC patients who have few comorbidities. Another limitation of our analysis is its inherent restriction to those trials for which patient-level data were provided to the ACCENT group (Supplementary Table S1, available at *Annals of Oncology* online). While ACCENT remains the single largest database of clinical trials for adjuvant therapy in CC created to date and contains patient data from most of the trials that have changed clinical practice, not every major randomized study in adjuvant CC is presently contained in ACCENT. At the same time, we note that our study offers strengths that would be difficult to achieve using individual population-based patient repositories as an alternative. Specifically, through use of the broadly multinational ACCENT database containing prospectively collected patient data from 41 countries, our work generalizes to cancer patients internationally as well as locally. The detailed and rigorous collection of covariates and outcomes within the included trials also strengthens confidence in our findings.

In conclusion, a large international comparison of the long-term survival of >30 000 CC patients contained in the ACCENT database with their expected survival from an MGP has revealed subgroups of patients who ultimately achieve post-treatment survival similar to individuals without cancer. These similarities occur relatively late, and are strongly dependent on the patient's disease not recurring, emphasizing the need for improved access to quality cancer care and continuing advances in treatment.

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disclosure

The authors have declared no conflicts of interest.

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Changes in the influence of lymphoma- and HIV-specific factors on outcomes in AIDS-related non-Hodgkin lymphoma

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Background: We undertook the present analysis to examine the shifting influence of prognostic factors in HIV-positive patients diagnosed with aggressive non-Hodgkin lymphoma (NHL) over the last two decades.

Patients and methods: We carried out a pooled analysis from an existing database of patients with AIDS-related lymphoma. Individual patient data had been obtained prior from prospective phase II or III clinical trials carried out between 1990 until 2010 in North America and Europe that studied chemo(immuno)therapy in HIV-positive patients diagnosed with AIDS-related lymphomas. Studies had been identified by a systematic review. We analyzed patient-level data for 1546 patients with AIDS-related lymphomas using logistic regression and Cox proportional hazard models to identify

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