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Pilleron, S., Charvat, H., Araghi, M., Arnold, M., Fidler-Benaoudia, M. M., Bardot, A., Guren, M. G., Tervonen, H., Little, A., O'Connell, D. L., Gavin, A., De, P., Aagaard Thomsen, L., Møller, B., Jackson, C., Bucher, O., Walsh, P. M., Vernon, S., Bray, F., & Soerjomataram, I. (2020). Age disparities in stage-specific colon cancer survival across seven countries: an ICBP SURVMARK-2 population-based study. *International Journal of Cancer*. https://doi.org/10.1002/ijc.33326

Published in:
International Journal of Cancer

Document Version:
Peer reviewed version

Age disparities in stage-specific colon cancer survival across seven countries: an ICBP SURVMARK-2 population-based study

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Abbreviations: EMH: excess mortality hazard; ICBP: International Cancer Benchmarking Partnership: PBCRs: population-based cancer registries; SEER: Surveillance, Epidemiology and End Results.

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Keywords: cancer survival, older adults, epidemiology, population-based cancer registry

List of abbreviations: EMH: Excess Mortality Hazard; ICBP: International Cancer Benchmarking Partnership; ICD: International Classification of Disease; PBCR: Population-Based Cancer Registry; SEER: Surveillance, Epidemiology and End Results.

ABSTRACT

We sought to understand the role of stage at diagnosis in observed age disparities in colon cancer survival among people aged 50-99 using population-based cancer registry data from seven high-income countries: Australia, Canada, Denmark, Ireland, New Zealand, Norway and the United Kingdom. We used colon cancer incidence data for the period 2010-2014. We estimated the three-year net survival, as well as the three-year net survival conditional on surviving at least six months and one year after diagnosis, by country and stage at diagnosis (categorised as localised, regional or distant) using flexible parametric excess hazard regression models. In all countries, increasing age was associated with lower net survival. For example, three-year net survival (95% confidence interval) was 81% (80 to 82) for 50-64 year olds and 58% (56 to 60) for 85-99 year olds in Australia, and 74% (73 to 74) and 39% (39 to 40) in the United Kingdom, respectively. Those with distant stage colon cancer had the largest difference in colon cancer survival between the youngest and the oldest patients. Excess mortality for the oldest patients with localised or regional cancers was observed during the first six months after diagnosis. Older patients diagnosed with localised (and in some countries regional) stage colon cancer who survived six months after diagnosis experienced the same survival as their younger counterparts. Further studies examining other prognostic clinical factors such as comorbidities and treatment, and socioeconomic factors are warranted to gain further understanding of the age disparities in colon cancer survival.

Novelty and Impact

We investigated how age disparities in colon cancer survival vary across stages at diagnosis using the most recent population-based cancer registry data in seven countries. Age disparities in survival were marked primarily in the first year after diagnosis and widened with the stage at diagnosis. We observed similar patterns across all countries. Early diagnosis and individualized management should help to reduce early mortality in older patients, and ultimately age disparities in colon cancer survival.

INTRODUCTION

Colon cancer is the fourth most frequently diagnosed cancer and the sixth most common cause of cancer death for adults aged 50 years and older worldwide.[1] Recently estimated five-year net survival for colon cancer ranged from 58.9% to 70.9% across six high-income countries.[2] Previous population-based studies highlighted substantial age differences in colon cancer survival with consistently lower survival for older adults (75+ years) compared with younger adults.[3–5] In addition, whilst colon cancer survival has improved over the past decades,[5,6] the improvement in survival lagged for older people, creating a larger age-gap in survival.[3,5] This reduced survival for older adults may be a consequence of socioeconomic (*i.e.* social isolation, disadvantaged groups or low socioeconomic status),[7,8] patient-related (*i.e.* comorbidities, frailty, lower tolerance of multi-modality treatments),[9,10] and healthcare-related (*i.e.* sub-optimal cancer management, diagnostic delays) factors.[11–13] These factors individually, or in combination, could contribute to colon cancer diagnosis through emergency care, and/or, more advanced cancer stage at diagnosis.[14] An important prognostic factor is the stage at diagnosis, but few studies to date have examined the effect of this factor on colon cancer survival by age group in different countries with similar access to health care.[15,16]

In this study, we have used the most recent population-based data from seven high-income countries with high-quality cancer registration as well as universal access to, and comparable expenditure on, healthcare (Australia, Canada, Denmark, Ireland, New Zealand, Norway and the United Kingdom) to examine age inequalities in colon cancer survival by stage at diagnosis among adults aged 50 years and older. To increase our understanding of age differences in colon cancer survival, we also

investigated the effect of age on excess mortality hazards across cancer stages at diagnosis for different follow-up times after diagnosis.

METHODS

Data sources

Incident cases of colon cancer (ICD-10 codes C18.0-C19.0) diagnosed between 2010 and 2014, as well as corresponding population and lifetable data, were obtained from 19 population-based cancer registries (PBCRs) in Australia (Victoria, New South Wales), Canada (all provinces except Québec), Denmark, Ireland (incidence data available up to 2013), New Zealand, Norway, and the United Kingdom (England, Wales, Northern Ireland, Scotland) from the International Cancer Benchmarking Partnership (ICBP) SURVMARK-2 study.[2] We excluded data from Western Australia (Australia) and Quebec (Canada) because they had no recorded stage data for our study period. We restricted our analyses to patients aged between 50 and 99 years old at diagnosis between 2010 and 2014. We defined multiple primary cancers following the International Association of Cancer Registries rules[17], and included only the first occurrence of colon cancer regardless of primary cancer diagnosis in another site. The age variable was complete at 100%. Only patients aged 50 and above were included as studies have shown that colon cancer features and management among younger adults are different compared with cancer diagnosed at older ages.[18,19] The study end date was 31 December 2015, except for the Canadian provinces of Ontario and Newfoundland for which the follow-up was only available to 31 December 2014. All data were cleaned and harmonised following a standardised protocol.[5] Patients were excluded if their diagnosis was based on death-certificate only (n=3,791; Supplementary Table), or survival time in days could

not be calculated because of missing day and month of diagnosis (n=21). We further excluded patients with *in situ* tumours (n=193).

Stage definition

Tumour stage at diagnosis was provided by all cancer registries where feasible according to the ICBP SURVMARK-2 study protocol. These data included: pathological, clinical, or registry T, N and M values; Surveillance, Epidemiology and End Results (SEER) summary stage, and/or Dukes' stage. A standard procedure to map all stage data to the SEER Summary Stage 2000 (SEER SS2000) was followed, to categorise cases into four groups: localised, regional, distant and missing stage.[20]

Statistical analysis

Three-year net survival estimation

Net survival (survival that would be observed if cancer patients could only die from their cancer) is typically used to assess survival for cancer patients. Because it takes into account the impact of competing causes of death that may largely differ between populations, it constitutes a useful indicator to compare the effectiveness of health services for different countries or periods of time.[21]

The estimation of net survival was based on the excess hazard approach: the total mortality hazard rate for cancer patients is assumed to be the sum of a cancer-specific hazard, the so-called "excess" hazard rate that accounts for the mortality directly or indirectly related to cancer, and an "expected" hazard rate describing mortality from other causes. In the absence of reliable cause of death information, the latter is derived from population lifetables and the former is estimated, in our case, through a flexible parametric regression model. For each PBCR, we obtained age-and sex-stratifed expected mortality rates at the end of the follow-up for each individual from lifetables for the years 2010-2015. For each country, the excess

mortality hazard for all stages combined and for each stage at diagnosis was fitted using a hazard regression model, with the logarithm of the baseline hazard described by a quadratic B-spline with one knot located at the median of the follow-up times for patients who died. The effect of (continuous) age on the excess hazard was assumed to be linear on the logarithmic scale. A non-proportional effect of age was modelled by including interaction terms between age and the B-spline bases describing the baseline hazard.

Sensitivity analyses

We analysed the impact on estimates of net survival due to missing information on stage at diagnosis using multiple imputation.[22] For each country, 30 imputed datasets were generated using the Multiple Imputation by Chained Equation procedure: missing stage values were imputed using a multinomial regression model including age at diagnosis, year of diagnosis, sex, vital status, and the Nelson-Aalen cumulative hazard estimate.[21] The modelling strategy described above was applied to the generated datasets and results were combined using Rubin's rule.

All statistical analyses were performed with R statistical software (version 3.4.0; R Development Core Team, 2017). In particular, we used the mexhaz R package to fit excess mortality hazards,[23] and the MICE R package for multiple imputation.[24]

RESULTS

Over the 2010-2014 period, we included 264,305 patients aged 50-99 (median age at diagnosis = 73, interquartile range 65-81; 47.6% were females) diagnosed with colon cancer in the seven countries.

Table 1 shows the number of cancer cases diagnosed in the period 2010-2014, the number of deaths that occurred by 31 December 2015, and the number of person-years of follow-up by stage, country and age group at diagnosis.

Overall, 29.6% of colon cancer cases were diagnosed with localised, 28.0% with regional, 19.0% with distant cancers and 23.4% had missing stage recorded. There were large differences in the percentage of cases with missing stage data across countries: 6.4% in Canada, 8.0% in Australia, 8.1% in Ireland, 10.0% in Norway, 11.1% in New Zealand, 16.0% in Denmark, and 37.3% in the United Kingdom.

The distribution of stage by age at diagnosis is shown in Figure 1. The percentage of missing stage was consistently higher for the oldest age group. Noteworthy, the percentage of distant stages was similar across all age groups in all countries. After imputation for missing stages, this was still the case (Supplementary Figure 1).

The estimated three-year net survival (95% confidence interval) was 71% (71 to 72) in Australia, 68% (67 to 68) in Canada, 67% (66 to 68) in Denmark, 60% (58 to 61) in Ireland, 64% (63 to 65) in New Zealand, 66% (65 to 67) in Norway and 58% (58 to 59) in the United Kingdom. The variation by age was significant in all countries with a consistently lower survival for older adults. For example, net survival was 81% (80 to 82) for 50-64 year olds and 58% (56 to 60) for 85-99 year olds in Australia, and 74% (73 to 74) and 39% (39 to 40) in the United Kingdom, respectively (Figure 2).

Figure 3 presents the estimated three-year net survival by age, stage at diagnosis and country. In all countries, three-year net survival markedly decreased with more advanced cancer stage regardless of age at diagnosis, with a more linear decline with age among distant-stage cases. Within each cancer stage, survival generally decreased with increasing age at diagnosis, with the greatest survival differences between age groups observed for those diagnosed with distant stage colon cancer. For those with missing stage recorded, estimated three -year net survival was similar to that for regional disease for younger patients and that for distant disease for older patients.

To better understand what is driving the estimated three-year net survival we examined the excess mortality hazard (EMH) for patients aged 55, 65, 75 and 85 years at diagnosis by stage at diagnosis in each country (Supplementary Figure 2). For each stage at diagnosis, we observed a similar pattern across countries. For patients diagnosed with localised stage, the EMH was highest in the first six months after diagnosis for all ages and incrementally increased with increasing age. Six months after diagnosis, the EMH for older aged people approached that for younger people. For patients diagnosed with regional stage, the EMH for those who were older was highest in the first year after diagnosis but the difference by age persisted over a longer time especially in Ireland and the United Kingdom. Finally, for patients diagnosed with distant stage, the curves for EMH for older patients and their younger counterparts converged at around 24 months after diagnosis.

Finally, we examined three-year net survival conditional on surviving one, three, six and 12 months (Figure 4 and Supplementary Figures 3-5) after diagnosis by age and stage at diagnosis and country. Age-related disparities were no longer evident if patients with localised disease survived six months after diagnosis and were considerably reduced if patients with regional stage survived six months after diagnosis.

The imputation for missing stage did not change our results for distant cancers, while it increased age disparities in 6-month, 1-year, and 3-year net survival for localized and regional cancers (supplementary Figures 6-11).

DISCUSSION

Using the most up-to-date data for patients diagnosed with colon cancer in 19 population-based cancer registries in seven high-income countries, we observed marked disparities in survival by age primarily in the first months after a colon cancer

diagnosis. We also demonstrated that age disparities in survival widened with the stage of disease at diagnosis in all countries investigated. Interestingly, similar patterns in age disparities in colon cancer survival were observed across all seven countries investigated.

Similar to Colonna and colleagues, we found that the difference in the excess mortality hazard for patients aged 75+ compared with younger patients was greatest in the initial year following diagnosis.[4] Our results by stage highlight this early excess mortality was observed across all stages of colon cancer and increased with the severity of the disease. Early death in older cancer patients may be explained by life-threatening comorbid conditions that are more prevalent in colon cancer patients than in the general population[9,25]. For localised and regional stages, surgery is the main treatment strategy; the excess risk among older adults may be a consequence of reduced likelihood of undergoing surgery because physicians may consider their patients too frail to undergo surgery[26], or the patient refused surgery[27,28]. Even if not free of bias, recent studies suggested lower survival in patients who refused surgery compared with those who did not[27,28]. Older patients had also higher post-operative mortality rates that have been linked to emergency surgery, surgical complications, and higher comorbidity levels.[29–32]

With appropriate perioperative risk stratification of older patients, complete geriatric assessment, and geriatric co-management, surgical outcomes for older patients may improve and more closely resemble those experienced by their younger counterparts.[33–35] For stage III colon cancer, adjuvant chemotherapy is recommended regardless of age, but monotherapy will be preferred for older patients.[36] Yet, studies have shown that older patients with regional stage colon cancer are less likely to receive chemotherapy than younger patients.[37–39] In general,

for advanced stage, it is recommended to use less intensive combination therapies for unfit older patients.[40] Some evidence suggests that fit older patients can be treated using the same chemotherapy regimens as younger adults. [41,42] In any case, cancer management should be individualised taking into account the health status and fitness of patients.[13] Better data on treatment and additional patients' characteristics (e.g. comorbidity or frailty), the diagnostic pathway, as well as social factors, would improve our understanding on the influence of these factors on older patients' survival.

The age-related survival gap was much wider when colon cancer was diagnosed at a more advanced stage. Social, clinical, or health-system-related factors may cause delays in cancer diagnosis for older patients.[12,43] Older adults are also more prone to be diagnosed through emergency settings, and this has been associated with a lower chance of curative treatment and excess risk of mortality, particularly in the initial months after diagnosis.[44] Also, the presence of comorbidities has been linked to the increased likelihood of diagnosis with metastatic stage.[45] Recent studies have shown that the diagnosis of advanced colorectal cancer was associated with longer intervals between commencement of symptoms and diagnosis, which in turn is related to older age and level of comorbidity.[43,46] A comprehensive understanding of factors related to the timely diagnosis of colon cancer for older patients is needed to be able to propose appropriate actions to increase earlier diagnosis and ultimately enhance chances of surviving their cancer.

The stage at diagnosis was missing for 6-37% of cases across countries. Two main reasons may explain missingness: administrative (or registration) problem or clinically uselessness. In the former, the bias would be limited because missingness is not linked to neither survival nor prognostic factors and may be considered as

missing at random. If the stage is incomplete in patients with specific characteristics (i.e. older age, late-stage, high comorbidity level)[45], missingness may lead to biased estimates. Unfortunately, we were unable to distinguish these two reasons due to lack of data e.g. comorbidity. Imputation has been reported a valid method for dealing with missing data, even when there are few variables with which to predict the missing values (i.e. only age in our case)[47].

The main strength of our study is that it includes seven high-income countries with information on cancer stage at diagnosis. A limitation is that there is potential for misclassification in our staging variable as it was developed by mapping a mixture of staging systems to the SEER SS2000. Indeed, we used broad stage categories, and possible stage differences across age groups may exist within these categories. Future studies investigating the age difference in stage misclassification are warranted. In addition, net survival was computed using lifetables, which are known to be less reliable for those at older ages. Another limitation relates to the possible misclassification of C19 cancers, which could actually be rectal cancers and thus potentially candidates for preoperative radiotherapy or chemotherapy plus radiotherapy. However, C19 cases represented a small percentage of total cases included (2.1%), and therefore bias is expected to be little and unlikely to lead to a different conclusion. We further acknowledge the lack of information regarding comorbidity, treatment, and specific geriatric variables such as cognitive status, frailty, and functional status, that could influence survival and the appropriateness of receiving treatment or not. As these variables are not routinely available in PBCRs, this limitation was unavoidable for this study, but does highlight a future area of needed research. Also, the results presented in this study may not be generalizable in other countries with different resources and health-care system. Finally, we

recognize that some geriatric patients may opt out of undergoing treatment in order to maintain their quality of life, despite the negative impact to their survival. However, analysing treatment preference was not feasible using administrative data such as PBCRs and was beyond the scope of this study.

CONCLUSION

In this international study, we have shown that the lower overall survival observed for older age groups is mainly explained by poorer survival for those with advanced disease (and to a lesser extent regional disease) at diagnosis and increased excess mortality in the first months after diagnosis. Even though it is unrealistic to eliminate the age disparity in colon cancer survival, improvements can still be made by eliminating unnecessary contributors to age disparities. Further studies examining other prognostic clinical factors (e.g. comorbidities, functional status, and geriatric conditions) and socioeconomic factors are warranted to gain further understanding of the age disparities in colon cancer survival.

Funding: This work was supported by Canadian Partnership Against Cancer; Cancer Council Victoria; Cancer Institute New South Wales; Cancer Research UK; Danish Cancer Society; National Cancer Registry Ireland; The Cancer Society of New Zealand; NHS England; Norwegian Cancer Society; Public Health Agency Northern Ireland, on behalf of the Northern Ireland Cancer Registry; The Scottish Government; Western Australia Department of Health; and the Wales Cancer Network. The work completed in this manuscript was undertaken whilst Sophie Pilleron was a post-doctoral fellow at the International Agency for Research on Cancer, which was partially funded by the European Commission's Seventh Framework Programme Marie Curie Actions – People – COFUND.

Role of the funder

The study sponsors had no role in the study design, data collection, data analysis, interpretation of data, writing of the report, and the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Conflict of interest

None.

Data Availability Statement

Data may be obtained from a third party and are not publicly available. The corresponding author should be contacted to for inquiries relating to potential access of data.

Acknowledgements

We would like to thank Lucie Hooper, Samantha Harrison, Charles Norell, Shanta Keshwala, Charlotte Lynch, Deborah Robinson and Irene Reguilon of Cancer Research UK for managing the programme. We would also like to thank the ICBP Local Leads, ICBP Programme Board, and ICBP Clinical Committees for their continuing support and advice, and the ICBP SurvMark-2 Academic Reference Group for providing independent peer review and advice for the study protocol and analysis plan development.

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