BMJ Oncology

Under-representation of older Indian persons with cancer in clinical trials

Vanita Noronha,[1] Vijay Patil,[2] Nandini Menon,[1] Manali Kolkur,[1] Zoya Peelay,[1] Minit Shah,[1] Vijayalakshmi Mathrudev,[1] Srushti Shah,[1] Kavita Nawale,[1] Nita S Nair,[3] Anant Ramaswamy,[1] Vikas Ostwal,[1] Sarbani Ghosh-Laskar,[4] Jai Prakash Agarwal,[4] Pankaj Chaturvedi,[5] Supriya Chopra,[4] Vedang Murthy,[4] Sheila N Myatra,[6] Jigeeshu Divatia,[6] Vikram Gota,[7] Sudeep Gupta,[1] Vikram Chaudhari,[5] Sabita Jiwnani,[5] Shailesh V Shrikhande,[5] Richa Vaish,[5] Devendra Chaukar,[8] Shivakumar Thiagarajan,[5] Sudhir Nair,[5] Anil D'Cruz,[3] Amey Oak,[9] Rohini Hawaladar,[10] Oindrila Roy Chowdhury,[1] Shripad Banavali,[1] Rajendra Badwe,[5] Kumar Prabhash [1]

To cite: Noronha V, Patil V, Menon N, *et al*. Under-representation of older Indian persons with cancer in clinical trials. *BMJ Oncology* 2024;**3**:e000445. doi:10.1136/bmjonc-2024-000445

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjonc-2024-000445).

Received 26 April 2024
Accepted 12 July 2024

For numbered affiliations see end of article.

Correspondence to
Dr Kumar Prabhash;
kumarprabhashtmh@gmail.com

ABSTRACT

Objective Older patients with cancer have traditionally been under-represented in global clinical trials. There are no data from India regarding this issue.

Methods and analysis This was a retrospective analysis done at our institute on interventional studies conducted between 2003 and 2023 in adult patients with malignancies. We excluded studies done exclusively in the paediatric population and observational studies.

Results We included 21 894 patients enrolled in 150 interventional trials from the departments of surgical, medical, and radiation oncology, anaesthesia, and clinical pharmacology; 110 (73.3%) were investigator initiated. There were 38 trials (25.3%) in breast cancer (6141 patients, 28%), and 33 (22%) in head and neck cancer (6975 patients, 31.9%). Studies were predominantly phase III (97 trials (64.7%)). Multicentric studies comprised approximately one-third (48, 32%). The median age of enrolled patients was 51 years (IQR 43–59). There were 5132 (23.4%) participants aged ≥60 years, 2678 (12.2%) ≥65 years and 1045 (4.8%) ≥70 years. Data from the hospital registry revealed that 30% of adult registrations were ≥60 years. There was a significant increase in the proportion of older patients enrolled in clinical trials from 2003 (8%) to 2019 (22%) compared with their proportion in the hospital registry (stable at 28%–29%); p<0.001.

Conclusion There is a gap between the proportion of older Indian adults with cancer in the hospital registry and those enrolled in interventional clinical trials, however, this gap has shrunk over time. Various factors that limit the recruitment of this vulnerable cohort like age-specific eligibility criteria are immediately actionable to make clinical trials more inclusive.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Older patients with cancer are traditionally under-represented in clinical trials globally; no data exist regarding their representation in interventional studies in India.

WHAT THIS STUDY ADDS

⇒ In a cohort of 21 894 adult patients recruited in interventional clinical trials, 23% were ≥60 years.

⇒ During the period of the study, 30% of adult patients registered at our institution were ≥60 years.

⇒ The proportion of older patients enrolled in clinical trials significantly increased from 2003 (8%) to 2019 (22%) compared with their proportion in the hospital registry (stable at 28%–29%); p<0.001.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Various factors that limit recruitment of this vulnerable cohort like age-specific eligibility criteria are immediately actionable to make clinical trials more inclusive.

INTRODUCTION

The government of India has defined an 'older person' as someone aged 60 years and over, as reflected by the retirement age,[1] and various programmes such as the National Program for Health Care of the Elderly[2] and the National Pension Scheme.[3] Other institutions in India as well as the National Cancer Registry Programme also follow this age cut-off of 60 years.[4–8] This lower age cut-off used in India to define the geriatric age group as compared with that used in Western countries like the USA (65 years, as reflected by the American Society of Clinical Oncology guidelines)[9] and Europe (70 years, as reflected by the European Society of Medical Oncology guidelines)[10] is primarily based on the life expectancy of the population. As of 2024, the estimated life expectancy in India is 72.03 years, whereas it is 79.74 years in the USA, and 84.38 years in Switzerland.[11] The life expectancy in other Southeast Asian countries is similar to that in India, and they,

therefore, follow the same age cut-off to define older individuals.

India's current projected population is 1.44 billion,[12] with approximately 10% of the population aged over 60 years.[13] As per data from the National Cancer Registry Programme of the Indian Council of Medical Research, 46.5% of the cancer cases registered with the 28 population-based cancer registries and 35.4% of the cases registered with the 98 hospital-based cancer registries were aged 60 years and over; globally, the proportion of older adults with cancer has been reported to be 66.3%.[7] Thus, although approximately 10% of India's population is in the geriatric age group, there is a disproportionately high number of older persons with cancer ranging between 35% and 46%. This group of older persons with cancer has traditionally been neglected in terms of both evaluation and therapy.[14 15]

Clinical trials serve as the cornerstone of evidence-based medicine. Our patient management decisions are based on the results of these clinical trials.[16] It is imperative that the patients we routinely see in the clinic are adequately represented in these trials. Additionally, enrolment in a clinical trial is a mechanism for patients to gain access to new and potentially lifesaving medications, which may not be widely available. Unfortunately, some subsets of patients have been less represented than others in clinical trials. Racial minorities and women have been found to be under-represented in clinical trials.[17] Similar under-representation has been noted for older persons with cancer. Various studies from the USA and Canada have reported that the representation of older persons with cancer in clinical trials ranges from 22% to 41%.[18–24]

High-income countries dominate the clinical research arena. An analysis of Cochrane reviews and randomised trials (797 reviews of 12 340 trials in 10 937 306 participants) done in non-communicable diseases (cardiovascular disorders, cancers, diabetes and chronic respiratory diseases) reported that 90% of clinical trials and over 80% of participants were from high-income countries. India, classified by the World Bank as a lower-middle-income country (LMIC),[25] along with other LMICs contributed 4.95% of trials (n=438) and 11.68% of participants.[26] Added to this dearth of clinical trials in LMICs, there is a complete lack of data on the representation of older persons with cancer in clinical trials in LMICs. We, therefore, performed this study to understand whether older patients with cancer have been adequately represented in clinical trials at our centre and whether we could identify any trend in enrolment over time, as well as any factors that impacted the enrolment of older Indian persons with cancer in interventional clinical trials.

METHODS

General study details

This was a retrospective analysis done at the Tata Memorial Hospital, a tertiary cancer centre in Mumbai, India. Our hospital is the leading cancer hospital in India, and we register patients from all over the country. As per our hospital registry data from 2023, a little over quarter of the patients registered (27.2%) were from Maharashtra (excluding Mumbai), and 12.6% were from Mumbai (Maharashtra). The rest of the cases registered at our institution were from across India, with the leading states including West Bengal in East India (16.6%) and Uttar Pradesh in North India (10.2%).

Patient and public involvement

There was no patient/public involvement in the design, conduct, reporting or dissemination plans of our research.

Participants

We included participants in interventional clinical studies that had been done at least partly at our institute, between 1 January 2003 and 1 May 2023. We excluded observational studies, and studies done exclusively in the paediatric population (age <18 years).

Aims/objectives

Our primary aim was to evaluate the percentage of older patients with cancer who were enrolled in interventional clinical trials at our institute, which we defined as the number of patients aged 60 years and over, enrolled in various interventional studies divided by the total number of patients recruited in interventional clinical trials. Our secondary endpoints were the proportion of older Indian patients with cancer enrolled in interventional clinical trials compared with the overall proportion of older patients with cancer registered at our centre, the number of studies that had inclusion or exclusion criteria that limited the enrolment of older patients on clinical trials, including an upper age limit of enrolment, performance status criteria and comorbidities. We also attempted to study the proportion of trials that included age as a stratification factor. We aimed to establish the relationship of various factors to clinical trial enrolment of older Indian patients with cancer, including sex, age, sponsor, treatment modality, treatment intent, centre, randomisation, age-specific eligibility criteria, age as a stratification factor, and clinical trial endpoints. Finally, we aimed to assess the time trend of enrolment of older persons with cancer in interventional clinical trials over the course of the study.

Study methodology

We contacted the principal investigators of the various studies and obtained information regarding the total number of patients enrolled, dates of enrolment, inclusion and exclusion criteria of the studies, individual participant data (age and sex) and details about the study, including the name, project number, phase, sponsor, type of intervention, primary tumour type, randomisation, stratification, and whether there was any preplanned age-specific analysis. The rationale to analyse age-based stratification and preplanned age-specific analysis was a collective decision of the investigators to explore this aspect. We thought that this may have indicated more cognizance/sensitivity to the patient's age at the time

of planning the study, and we wondered whether this may have impacted the enrolment of older patients with cancer. Data were collected in a Microsoft Excel sheet. The cut-off selected for older patients was 60 years and over, as is followed in our geriatric oncology clinic.[27]

Statistics

No formal sample size was calculated. We included all the studies that we were able to obtain information. The data were analysed in the Statistical Package for the Social Sciences (IBM, Released 2015. IBM SPSS Statistics for Windows, V.23.0., IBM).

The primary outcome, that is, the proportion of older patients with cancer enrolled in interventional clinical trials was calculated as follows:

$$\frac{\text{Number of patients aged 60 years and over enrolled in interventional clinical studies}}{\text{Total number of patients recruited in those studies}}$$

To calculate the proportion of older Indian patients with cancer enrolled in interventional clinical trials compared with the overall proportion of older patients with cancer, we calculated what percentage of adults (aged ≥18 years) with cancer registered at our hospital were aged ≥60 years during the time frame of the study. We obtained this information from our hospital-based cancer registry. We compared the proportion of older adults with cancer enrolled in interventional clinical trials to the proportion of the total adult patients with cancer during that time frame. We similarly calculated the proportion of patients aged ≥65 years, and ≥70 years, and estimated the representation of these cohorts of patients in interventional clinical trials and then compared them to the corresponding proportions in the hospital-based cancer registry. We calculated the number of clinical trials with stringent eligibility criteria (eg, an upper age limit) divided by the total number of clinical trials evaluated. We followed a similar process to calculate the proportion of trials that included age as a stratification factor. The above endpoints were reported as absolute numbers and simple percentages. The effects of various factors on enrolment of older Indian patients with cancer in interventional clinical trials were tested using univariate logistic regression analysis, expressed as OR with the 95% CI and graphically represented as a forest plot. In order to calculate the time trend of enrolment, we compared the proportion of patients aged ≥60 years in clinical trials for each year to the proportion of these older patients with cancer in the hospital registry for the same year using χ^2 test. A $p<0.05$ was considered statistically significant.

RESULTS

We included the data of 21 894 patients enrolled in 150 interventional clinical trials that were conducted between September 2003 and April 2023. None of the studies had been conducted exclusively in older adults, and none had been conducted in the geriatric oncology clinic. Most of the multicentric studies were pharma-sponsored global studies. The details of the trials included are provided in table 1. The median age of the participants was 51 years (IQR 43–59). There were 5132 patients (23.4%) who were ≥60 years, 2678 (12.2%) aged ≥65 years and 1045 (4.8%) ≥70 years. Between 2003 and 2022 (excluding 5 years for which data were not available in the hospital registry, ie, 2009–2011 and 2015–2016) there were 323 356 adult patients (aged ≥18 years) registered at our institution. Of these, 97 002 (30%) were aged ≥60 years (figure 1).

The distribution of older patients with cancer according to the primary tumour, both overall and in those enrolled in clinical trials is depicted in online supplemental figure 1. The greatest differences between the proportion of patients enrolled in clinical trials as compared with their occurrence in the hospital registry were for oesophagogastric and gynaecological cancers. Interestingly, there was an excess enrolment of older adults in the urooncological trials, that is, prostate, bladder and kidney cancers as compared with the proportion in the hospital registry for those tumours.

In 38 trials (25.3%), the eligibility criteria specified an upper age limit, which was set at 60 years in one trial (0.7%), 65 years (8%) in 12, 70 years in 14 (9.3%), 75 years in seven (4.7%) and 80 years in four trials (2.7%). Eastern Cooperative Oncology Group performance status of 2 was an exclusion criterion in 38 (25.3%) trials while 95 (63.3%) trials excluded patients with uncontrolled comorbidities. In two trials (1.3%), illiteracy was an exclusion criterion. The various trials at our institute were planned and written by different investigators at different time points and for different malignancies. The eligibility criteria were decided either by the individual investigator in the case of investigator-initiated trials or by a central steering committee in the case of sponsored trials. The actual eligibility criteria, including the decision regarding an upper age limit for enrolment, would have depended on multiple factors including the primary malignancy, stage of the disease, type of study, therapy planned, the disease management group, department, ethics committee and various other factors, including the discretion and overall philosophy of the planning committee. This is probably why different age cut-offs for the upper age limit were decided for various trials.

The proportion of older persons with cancer enrolled in various types of studies, based on different factors, is depicted in figure 2. Of the 150 trials included, there were 87 trials (58%) conducted in 10 497 patients (47.9%) on systemic therapy. We broadly divided systemic therapy into oral (hormonal therapy, oral targeted therapy, oral chemotherapy; 17 trials (20%)), intravenous cytotoxic therapy; 57 trials (66%) and intravenous non-cytotoxic therapy (immunotherapy, targeted therapy; 13 trials (15%)). The most toxic therapy being administered was used for classification. For example, a randomised trial in which oral metronomic chemotherapy was compared with intravenous chemotherapy was coded as an intravenous chemotherapy trial (as enrolled patients would

Table 1 Details of the trials and the enrolled participants included in the study on representation of older adults with cancer in interventional clinical trials at our institute

Category	Subcategory	Number of trials (%)	Number of participants (%)	Participants aged 60 years and over, in number (%)	Participants aged 65 years and over, in number (%)	Participants aged 70 years and over, in number (%)
Overall	–	150	21 894	5132 (23.4)	2678 (12.2)	1045 (4.8)
Treatment modality	Medical oncology	92 (61.3)	9611 (43.9)	2646 (27.5)	1389 (14.5)	551 (5.7)
	Surgical oncology	31 (20.7)	8515 (38.9)	1578 (18.5)	753 (8.8)	221 (2.6)
	Radiation oncology	14 (9.3)	2841 (13.0)	674 (23.7)	403 (14.2)	211 (7.4)
	Anaesthesia	10 (6.7)	869 (4.0)	215 (24.7)	123 (14.2)	59 (6.8)
	Clinical pharmacology	3 (2)	58 (0.3)	19 (32.8)	10 (17.2)	3 (5.2)
Sponsor	Investigator initiated	110 (73.3)	20 831 (95.1)	4854 (23.3)	2513 (12.1)	971 (4.5)
	Pharmaceutical company	40 (26.7)	1063 (4.9)	278 (26.2)	165 (15.5)	74 (7)
Intent of therapy	Curative	73 (48.7)	15 617 (71.3)	3339 (21.4)	1704 (10.9)	648 (4.2)
	Palliative	56 (37.3)	4607 (21.0)	1391 (30.2)	746 (16.2)	305 (6.6)
	Not applicable (supportive care clinical trial)	21 (14.0)	1670 (7.6)	402 (24.1)	228 (13.7)	92 (5.5)
Centre	Single centre	102 (68)	20 382 (93.1)	4525 (22.2)	2276 (11.2)	815 (4)
	Multicentric	48 (32)	1512 (6.9)	607 (40.2)	402 (26.6)	230 (15.2)
Phase	Phase I	2 (1.3)	34 (0.2)	9 (26.5)	5 (14.7)	1 (2.9)
	Phase II	18 (12)	975 (4.5)	173 (17.7)	76 (7.8)	24 (2.5)
	Phase IIII	97 (64.7)	17 876 (81.7)	4226 (23.6)	2177 (12.2)	851 (4.8)
	Phase IV	11 (7.3)	153 (0.7)	34 (22.2)	17 (11.1)	7 (4.6)
	Not applicable	22 (14.7)	2856 (13.1)	676 (23.7)	400 (14)	160 (5.6)
Sex	Male	NA	10 477 (47.9)	2969 (28.3)	1644 (15.7)	704 (6.7)
	Female	NA	11 417 (52.1)	2163 (18.9)	1034 (9.1)	341 (3)
Primary tumour	Breast	38 (25.3)	6141 (28)	1011 (16.5)	474 (7.7)	135 (2.2)
	Head and neck	33 (22)	6975 (31.9)	1482 (21.2)	771 (11.1)	294 (4.2)
	Lung	21 (14)	2443 (11.2)	945 (38.7)	532 (21.8)	239 (9.8)
	Oesophagus	8 (5.3)	1830 (8.4)	576 (31.5)	272 (14.9)	83 (4.5)
	Stomach	3 (2)	455 (2.1)	108 (23.7)	58 (12.8)	23 (5.1)
	Hepatopancreaticobiliary	7 (4.7)	270 (1.2)	77 (28.5)	37 (13.7)	14 (5.2)
	Male genitourinary (prostate, penis)	4 (2.7)	247 (1.1)	214 (86.6)	184 (74.5)	134 (54.3)
	Kidney	2 (1.3)	31 (0.1)	12 (38.7)	6 (19.4)	2 (6.5)
	Bladder	1 (0.7)	92 (0.4)	50 (54.4)	31 (33.7)	14 (15.2)
	Gynaecologic	13 (8.7)	1872 (8.6)	319 (17)	129 (6.9)	34 (1.8)
	Glioma	3 (2)	252 (1.2)	21 (8.3)	8 (3.2)	0 (0)
	Multiple tumours	17 (11.3)	1285 (5.9)	317 (24.7)	176 (13.7)	73 (5.7)

NA, not applicable.

have to be fit for intravenous cytotoxic chemotherapy). Similarly, studies in which oral medications were added to standard intravenous chemotherapy were categorised as intravenous cytotoxic chemotherapy studies. There was a significantly higher proportion of patients aged ≥60 years in trials investigating oral therapy (339 of a total of 1101; 34%), compared with intravenous cytotoxic chemotherapy (1974 of a total of 8355; 24%) and intravenous non-cytotoxic anticancer therapy (263 of 1131; 23%); p<0.001 (figure 3I).

On univariate logistic regression (figure 3), the factors associated with significantly lower odds of enrolling older patients with cancer were age-specific eligibility criteria (OR 0.45; 95% CI 0.42 to 0.49; p<0.001), female sex of the participant (OR 0.59; 95% CI 0.55 to 0.63; p<0.001), trials conducted in the curative setting (OR 0.63; 95% CI 0.58 to

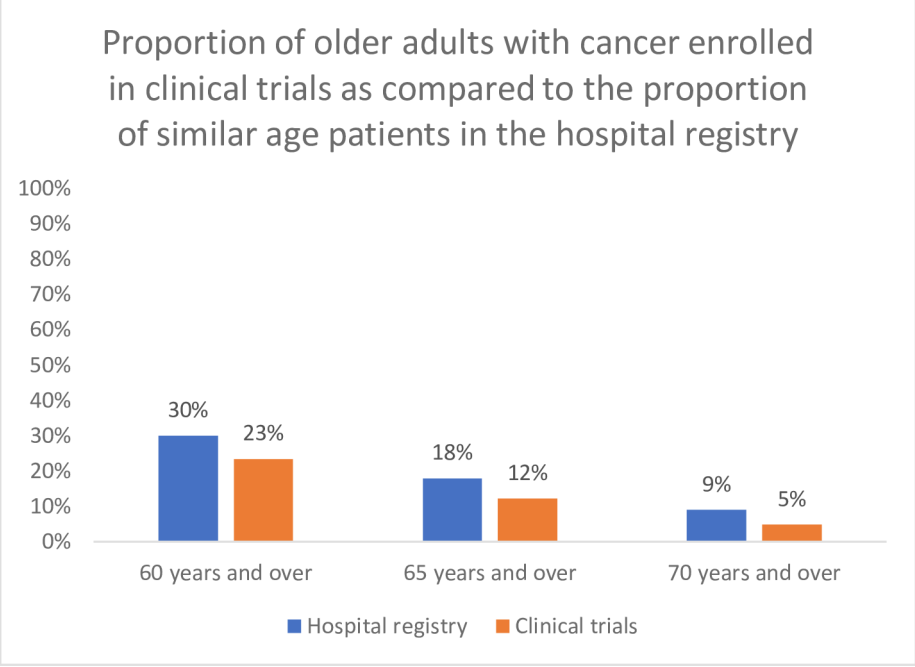

Figure 1 Proportion of older adults with cancer enrolled in clinical trials as compared with the proportion of similar age patients in the hospital registry.

0.68; p<0.001), trials across various treatment intents (eg, supportive care) (OR 0.73; 95% CI 0.64 to 0.83; p<0.001), investigator-initiated trials (OR 0.86; 95% CI 0.75 to 0.99; p=0.033), single-centre studies (OR 0.43; 95% CI 0.38 to 0.47; p<0.001) and the absence of quality of life (QoL) as a trial endpoint (OR 0.59; 95% CI 0.55 to 0.63; p<0.001).

To assess the time trend of recruitment of older Indian patients with cancer in interventional clinical trials (figure 4), we included 9807 patients (44.8%) who had been recruited in 65 trials (43.3%) between 2003 and 2019, as we had the enrolment dates for these. Although the proportion of older patients with cancer registered at our hospital remained relatively stable at 28%–29% throughout the course of the study, there was a steady increase in the proportion of older patients recruited, from 8% in 2003 to 22% in 2019. Comparing the proportion of older patients in clinical trials to the proportion overall in the hospital registry, there was a significant increase from the start to the end of the study; p<0.001. There did not appear to be a significant time trend in the proportion of interventional clinical trials that had age-specific exclusion criteria (online supplemental figure 2).

DISCUSSION

We found that although older patients with cancer comprised approximately one-third of the hospital registrations, they constituted only 23% of the participants in interventional clinical trials. Thus, there is a gap between the proportion of older persons with cancer registered at our hospital and the proportion enrolled in interventional clinical trials, which suggests that the evidence generated by these trials may or may not be entirely applicable to them. Older persons with cancer constitute a unique demographic with special challenges including issues with functionality, pharmacodynamics and pharmacokinetics with resultant dosing and toxicity issues, organ dysfunction and comorbidities, polypharmacy and drug interactions. Thus, deciding the optimal treatment for these vulnerable individuals is difficult and must be based on robust evidence. Under-representation in clinical research compounds the challenges in making appropriate evidence-based treatment decisions for these patients. Designing clinical trials exclusively for older patients with cancer would be ideal, however, this would be impractical and perhaps, impossible to do in all clinical situations and would involve excessive expense, manpower and infrastructure. The next best option would be to include these older patients in general clinical trials that recruit a broad base of patients. Hearteningly, our study revealed that the gap between the representation of older patients with cancer in clinical trials and that in the overall pool of patients seen in the hospital has been significantly shrinking over time, despite the fact that there have not been any formal interventions over the study period at our institution that could have contributed to this increase in enrolment. This increase is possibly attributable to a gradual recognition of the importance of geriatric oncology resulting from advocacy and a general increase in knowledge about older patients with cancer and reflected in the establishment of a dedicated geriatric oncology clinic at our centre in 2018.[28]

Various other studies have examined the representation in clinical research studies of older persons with cancer. In 2003, Lewis *et al* reported that 32% of participants in cooperative group clinical trials sponsored by the National Cancer Institute between 1997 and 2000 were ≥65 years,

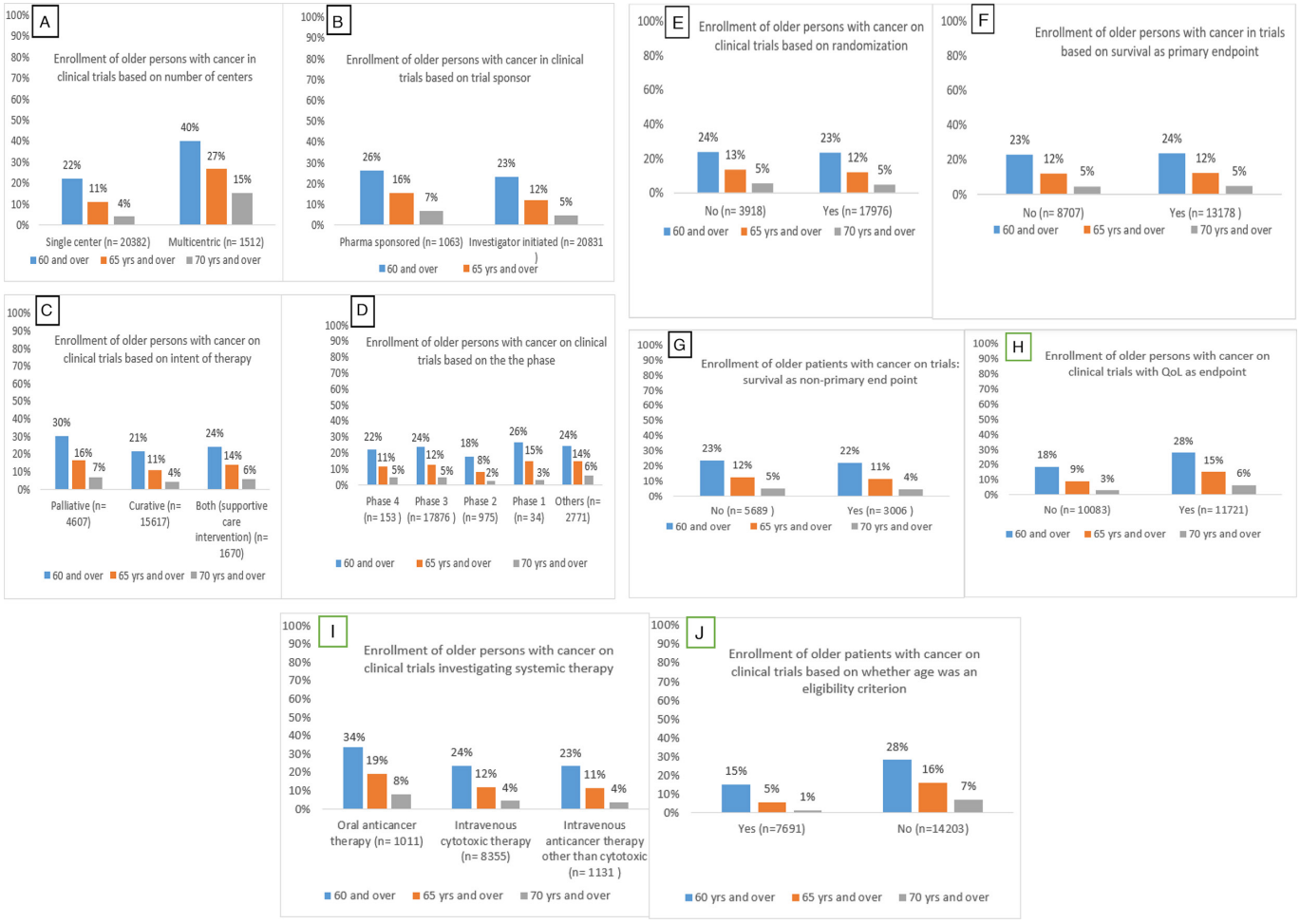

Figure 2 Enrolment of older persons with cancer in clinical trials in various age categories, according to various factors: (A) centres at which the trials were conducted, that is, single centre versus multicentric; (B) trial sponsor: pharmaceutical company sponsored, versus investigator initiated; (C) intent of therapy: curative, versus palliative, versus not specified (supportive care, etc); (D) phase of the study (phase I vs II vs III vs IV vs others; (E) whether the trial was randomised (yes vs no); (F) whether survival was the primary endpoint of the study (yes vs no); (G) whether survival was a secondary endpoint (yes vs no); (H) whether quality of life (QoL) was an endpoint; (I) type of systemic therapy (oral vs intravenous cytotoxic vs intravenous anticancer medicines other than cytotoxic like immunotherapy and targeted therapy) and (J) age as part of eligibility criteria (yes vs no).

as compared with 61% of incident cancer cases in the American population.[21] It is pertinent to note that we compared the representation of older adults with cancer in clinical trials to their proportion in our hospital-based cancer registry. However, data from the National Cancer Registry of India suggest that approximately 46.5% of patients with cancer in the population-based cancer registries and 35.4% in the hospital-based cancer registries are ≥60 years, which is relatively similar to the proportion noted in our hospital registry.[7] Talarico *et al* had reported that 36% of patients enrolled in drug registration trials of the US Food and Drug Administration (USFDA) between 1995 and 2002 were ≥65 years, compared with 60% in the US population.[19] A follow-up analysis by Singh *et al* for new drug approval trials by the USFDA between 2005 and 2013 revealed that hearteningly, 41% of participants were ≥65 years, compared with 56% in the US population, possibly suggesting a narrowing of the representation gap, similar to what was suggested by our study.[22] However, patients aged ≥70 years continued to be significantly under-represented: 24% in USFDA drug registration trials compared with 42% in the general US population. In our study, the proportion of patients ≥70 years was very low, both in the hospital-based cancer registry (9%), as well as in the interventional clinical trials (5%). Hutchins *et al* reported that 25% of patients enrolled in Southwest Oncology Group (SWOG) treatment trials between 1993 and 1996 were ≥65 years, compared with 63% in the US population.[23] Unger *et al* updated the analysis to include trials from 1997 to 2002 and reported that 31% of patients enrolled in SWOG trials were aged ≥65 years, compared with 61% in the Surveillance, Epidemiology and End Results (SEER) Programme, again suggesting that enrolment of older persons with cancer in clinical trials has increased over time.[24] All of these studies were conducted in the USA and therefore used an age cut-off of 65 years to define the geriatric age group. Comparing our study results in which we used an age cut-off of 60

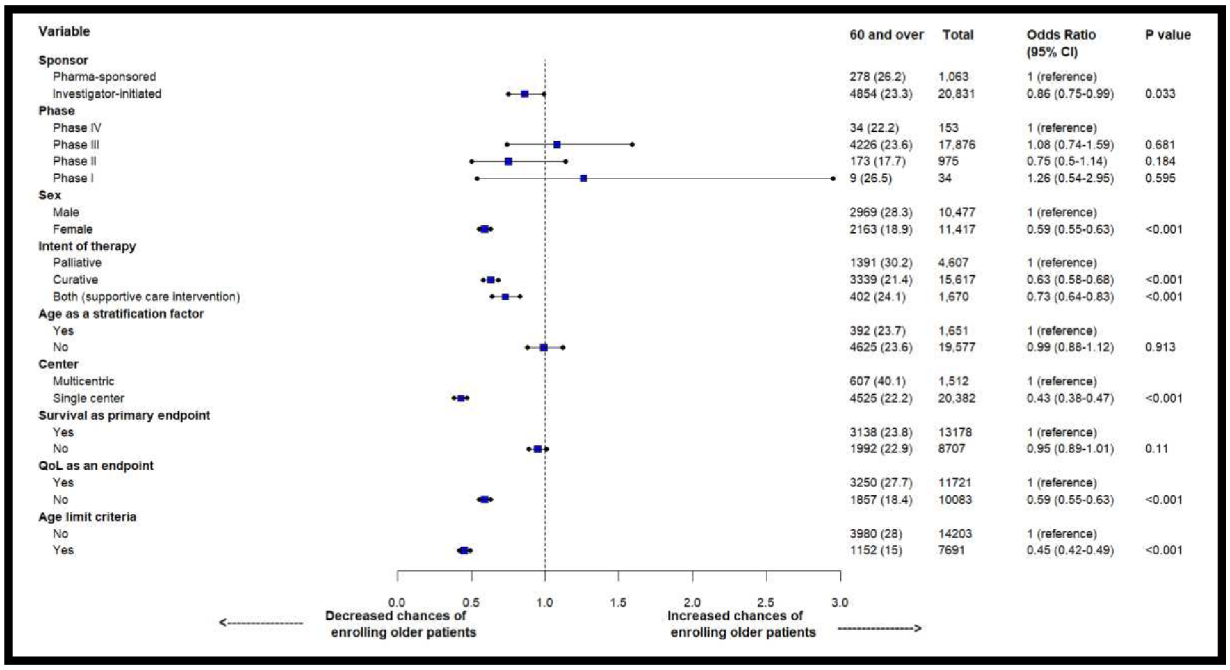

Figure 3 Univariate logistic regression to evaluate the factors that impacted the recruitment of older adults with cancer in interventional clinical trials.

years to these American studies may seem inappropriate, however, this was a comparison of enrolment of a geriatric cohort in two different populations, regardless of the age cut-off used. In general, it is the physiological age rather than the chronologic age that determines the geriatric age cut-off.[2929] In the absence of studies done in countries that have used 60 years as the age cut-off, we considered that this was the best method of comparing the data to give us an idea regarding the difference in representation of older patients with cancer in clinical trials conducted around the world.

We found that several factors impacted the recruitment of older patients with cancer in clinical trials. Some of these factors were actionable, for example, studies

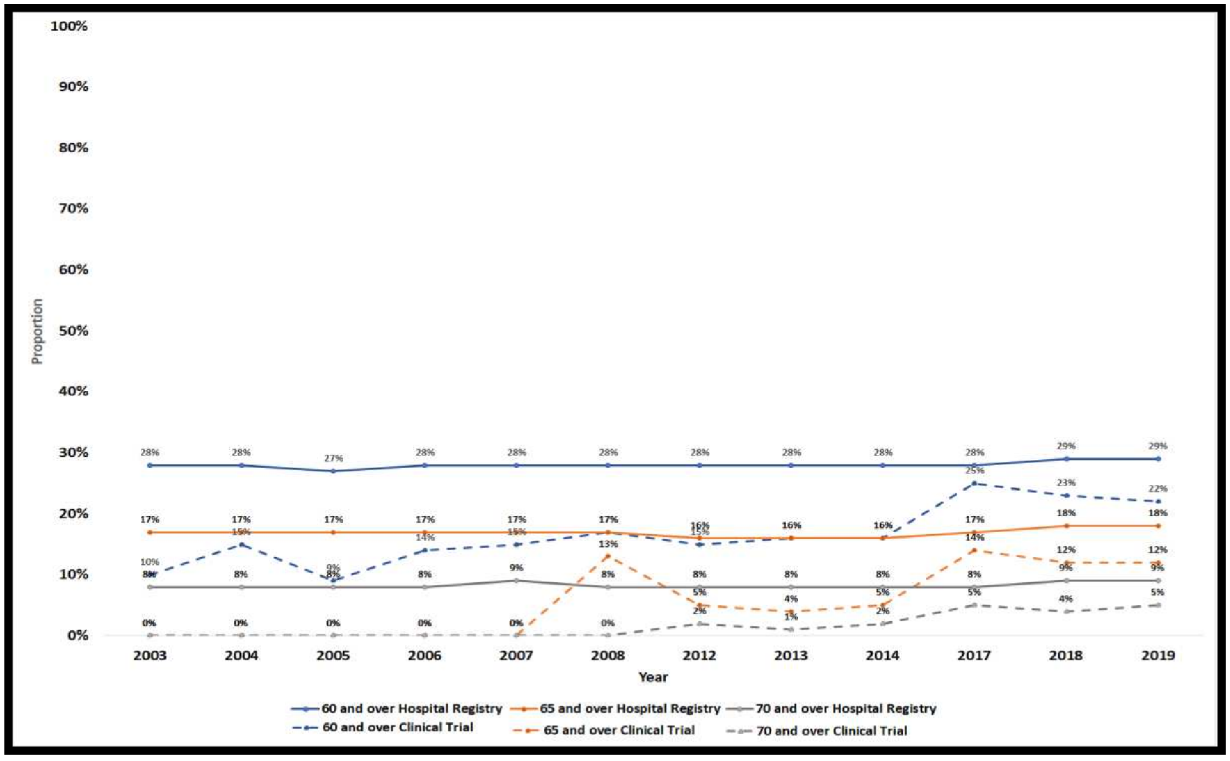

Figure 4 The time trend of the proportion of older adults with cancer enrolled in interventional clinical trials as compared with the proportion in the hospital registry over time.

without an upper age limit in the eligibility criteria and multicentric studies were far more likely to recruit older persons. This suggests that through some simple methods (doing away with upper age eligibility criteria) and some more complex methods (expanding single centre studies to make them multicentric), it may be possible to make studies more inclusive and increase the representation of older persons with cancer in clinical trials. Some factors that predicted less recruitment of older patients like sex of the participant (older women with cancer were most under-represented in clinical trials), curative setting trials and trials evaluating intravenous systemic therapy were not immediately actionable, and these would perhaps require continued advocacy and change in the mindset of investigators as well as patients. Kimmick *et al* conducted a randomised trial to evaluate whether it was possible to increase the recruitment of older patients in Cancer and Leukaemia Group B (CALGB) trials through a geriatric educational intervention. They found that the educational intervention failed to result in a significant increase in enrolment, and they suggested that much more would need to be done to bring about a change in physician and patient behaviour.[20] Sedrak *et al* recently published a systematic review on barriers to clinical trial participation of older patients with cancer, and interventions to improve recruitment.[30] They characterised the barriers to participation as system level (stringent eligibility criteria, language used in the consent form, appropriate trial availability), provider level (reluctance to enrol older patients for various reasons, time and personnel constraints, lack of awareness, etc), patient level (lack of knowledge, transportation issues, time constraints, concerns about efficacy and toxicity, treatment preferences, financial problems, emotional issues and lack of self-belief) and caregiver level (caregiver concerns and caregiver burden). The authors suggested various methods to increase the trial participation of older persons with cancer, including 'geriatricisation of trial design' (designing trials specifically for older patients, expanding the trial design and various other trial design modifications like adaptive design, prospective cohort, embedded study), measurement of relevant endpoints including QoL (which we also found to be impactful in our study) and overall treatment utility, expansion of the trial eligibility criteria, addressing barriers at the clinical trial site or at the stakeholder level, designing pragmatic studies and leveraging real-world data. Recently, Bertagnolli and Singh published a call to action with various recommendations to eliminate the under-representation of older patients in cancer clinical trials.[31] By studying the representation and factors affecting this representation at our institution, we hope to be taking the first step towards closing this evidence gap. Implementing any institution-wide change to increase the representation of older adults with cancer in interventional clinical trials would be challenging, however, perhaps the easiest and most feasible would be a mandate that the IEC questions the requirement for an upper age limit in the eligibility criteria, as long as the study intervention is not contraindicated in older adults with cancer.

Our study was limited by the fact that it was conducted at a single institution, and therefore, may not be reflective of the representation of older adults with cancer in clinical trials across India. For the purpose of this study, we sent emails to all the investigators from the institution and requested them to share the data of the studies that they had conducted; not all the investigators responded. We included the data of the investigators who responded and shared their data. We were unable to access the information regarding the studies that were not included in the analysis, or the total number of studies done in the institution. However, considering the large number of patients and trials included in the study as well as the fact that we included the data from multiple primary disease sites, and from different departments, we consider that the studies included in our analysis were likely to be representative of the overall pool of patients from our institution. The data from our hospital-based cancer registry are still in the process of being extracted, and were not available for 5 years (2009–2011 and 2015–2016). We will attempt to expand this study and obtain more complete data in the future. We compared the representation of older patients with cancer to their proportion in our hospital-based cancer registry, as we considered this to be the true denominator. However, other similar studies have used the proportion of older patients with cancer in the general population as the denominator. It appears that the proportion of older patients with cancer in the Indian population (between 35% and 46%) is only slightly higher than the proportion registered at our centre (30%), and therefore, using the denominator of the proportion in the general population would likely not have substantially changed the interpretation of our findings. We were able to obtain the dates of recruitment for little under half of the total cohort, and we used this data to determine the time trend for enrolment of patients in clinical trials at our centre. This may have introduced some bias in the time trend assessment. We found a 7% gap between the enrolment of older patients with cancer in interventional clinical trials to the proportion in the hospital-based cancer registry. Whether the gap between the proportion registered and the proportion enrolled truly signifies under-representation would have required a comparison to similar data from other institutions in India (which we were unable to find in the published literature), or a comparison to the enrolment of a younger cohort of patients, which was beyond the scope of our study. Unfortunately, an evaluation of the reasons why the number of older persons with cancer enrolled at our institute over the past few years has not increased commensurate with the increase in the number of older persons in India, was beyond the scope of our study. We found that pharma-sponsored studies had better representation of older patients with cancer than investigator-initiated studies. Most of the pharma-sponsored studies were global studies. It was our observation that these

studies usually did not have an upper age limit in the eligibility criteria, which is probably the reason for the better representation of older adults as compared with investigator-initiated studies. The reason for the difference in the eligibility criteria between pharma sponsored and investigator-initiated studies was unclear. It is possible that sociocultural factors may have influenced enrolment, especially considering the fact that the lowest representation of older adults with cancer in interventional clinical trials was noted in women and for patients with gynaecological malignancies. However, it was beyond the scope of our study to characterise these factors. We hope to be able to investigate this in a more systematic manner in the future. Although we evaluated the factors that impacted the representation of older patients with cancer in clinical trials, it was beyond the scope of our study to assess whether addressing those factors may have resulted in higher recruitment.

CONCLUSION

There is a gap between the representation of older Indian adults with cancer in interventional clinical trials, as compared with their proportion in the hospital registry. Various factors may affect this under-representation, some of which are actionable and could be modified to increase recruitment. The representation of older adults with cancer has significantly increased over time. Adequate representation of older adults with cancer in clinical research is a critical factor in deciding the optimal cancer-directed therapy for this group of vulnerable individuals.

Author affiliations
[1]Medical Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[2]Medical Oncology, PD Hinduja National Hospital and Medical Research Centre, Mumbai, Maharashtra, India
[3]Surgical Oncology, Apollo Cancer Centre, Mumbai, Maharashtra, India
[4]Radiation Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[5]Surgical Oncology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[6]Anaesthesiology, Critical Care and Pain, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[7]Clinical Pharmacology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[8]Surgical Oncology, Nanavati Max Institute of Cancer Care, Mumbai, Maharashtra, India
[9]Center for Cancer Epidemiology, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India
[10]Clinical Research Secretariat, Tata Memorial Hospital, Tata Memorial Centre, Homi Bhabha National Institute, Mumbai, Maharashtra, India

X Vedang Murthy @VedamgMurthy and Vikram Chaudhari @DrVAChaudhari

Acknowledgements The CARinG Health Services Core members (Supriya Mohile, Melissa Wong, Lisa Lowenstein, John Simmons, Harvey Cohen, Meghan Karaturi, Manvi Sharma, Cara McDermott, Jennifer Lund, Louise Walter, Hussai Nuristani, and Shuhan Yang) who gave valuable inputs while planning the study.

Contributors VN and KP were responsible for the conception and design of the study. All authors were responsible for acquisition of the data. VN, KP, ORC and RB were responsible for analysis of the data. All authors were responsible for interpretation of the data. VN drafted the article, and all other authors revised it critically for important intellectual content. VN and KP accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This was a retrospective analysis done at the Tata Memorial Hospital, a tertiary cancer centre in Mumbai, India. The study (project 3762) was approved by the Institutional Ethics Committee (IEC) of the Tata Memorial Hospital on 15 September 2021. Since it was a retrospective study with less than minimal risk to the participants and since there was no direct contact between the investigators and the study participants, the IEC waived the requirement to obtain written informed consent. The study was not registered with a publicly accessible clinical trials database like the Clinical Trials Registry-India, as this registers only prospective studies.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available on reasonable request. The individual deidentified data will be available on request to the corresponding author, KP (kumarprabhashtmh@gmail.com), until 5 years after publication. Requests beyond this time frame will be considered on a case-by-case basis.

ORCID iD
Kumar Prabhash http://orcid.org/0000-0001-8858-5004

REFERENCES

1 Centralized Circular Information System. Available: https://documents.doptcirculars.nic.in/D2/D02est/25012_8_98-Estt-A.pdf [Accessed 14 Jun 2024].
2 Ministry of Health & Family Welfare. Available: https://main.mohfw.gov.in/sites/default/files/detailed%20breif%20of%20NPHCE.pdf [Accessed 14 Jun 2024].
3 eNPS. Available: https://enps.nsdl.com/eNPS/NationalPensionSystem.html [Accessed 14 Jun 2024].
4 Bhagwasia M, Rao AR, Banerjee J, *et al*. Defining anthropometric thresholds (mid-arm circumference and calf circumference) in older adults residing in the community: a cross-sectional analysis using data from the population representative longitudinal aging study in India (LASI DAD). *BMJ Open* 2023;13:e077530.
5 Soni N, Banerjee J, Gunasekaran V, *et al*. Association of geriatric syndromes in older adults with chronic obstructive pulmonary disease. *Aging Med (Milton)* 2022;5:106–12.
6 Sansar B, Gupta A, Chitre A, *et al*. At crossroads: the challenges for geriatric oncology in India. *S Asian J Cancer* 2024.
7 Sankarapillai J, Krishnan S, Ramamoorthy T, *et al*. Epidemiology of cancers among older adults in India: findings from the national cancer registry programme. *Pub Health (Fairfax)* 2023;223:230–9.
8 Soni N, Banerjee J, Saravanan M, *et al*. Health-related quality of life in treatment-naive, older patients with cancer from India: a prospective observational study. *Cancer Res Stat Treat* 2022;5:474.

9 Dale W, Klepin HD, Williams GR, *et al*. Practical assessment and management of vulnerabilities in older patients receiving systemic cancer therapy: ASCO guideline update. *J Clin Oncol* 2023;41:4293–312.
10 European Society for Medical Oncology. Available: https://oncologypro.esmo.org/education-library/esmo-e-learning-and-v-learning/geriatric-oncology-an-introduction [Accessed 16 Jun 2024].
11 Worldometers. Available: https://www.worldometers.info/demographics/life-expectancy [Accessed 14 Jun 2024].
12 Statistics Times. Available: http://statisticstimes.com/demographics/country/india-population.php [Accessed 06 Jun 2024].
13 Statista. Available: https://www.statista.com/chart/30958/share-of-age-groups-in-indian-population [Accessed 15 Jun 2024].
14 Noronha V, Talreja V, Joshi A, *et al*. Survey for geriatric assessment in practicing oncologists in India. *Cancer Res Stat Treat* 2019;2:232.
15 Parikh P, Chaitanya K, Boppana M, *et al*. Geriatric oncology landscape in India – current scenario and future projections. *Cancer Res Stat Treat* 2020;3:296.
16 Noronha V. Making a case for cancer research in India. *Cancer Res Stat Treat* 2018;1:71.
17 Duma N, Vera Aguilera J, Paludo J, *et al*. Representation of minorities and women in oncology clinical trials: review of the past 14 years. *J Oncol Pract* 2018;14:e1–10.
18 Kemeny MM, Peterson BL, Kornblith AB, *et al*. Barriers to clinical trial participation by older women with breast cancer. *J Clin Oncol* 2003;21:2268–75.
19 Talarico L, Chen G, Pazdur R. Enrollment of elderly patients in clinical trials for cancer drug registration: a 7-year experience by the US food and drug administration. *J Clin Oncol* 2004;22:4626–31.
20 Kimmick GG, Peterson BL, Kornblith AB, *et al*. Improving accrual of older persons to cancer treatment trials: a randomized trial comparing an educational intervention with standard information: CALGB 360001. *J Clin Oncol* 2005;23:2201–7.
21 Lewis JH, Kilgore ML, Goldman DP, *et al*. Participation of patients 65 years of age or older in cancer clinical trials. *J Clin Oncol* 2003;21:1383–9.
22 Singh H, Kanapuru B, Smith C, *et al*. FDA analysis of enrollment of older adults in clinical trials for cancer drug registration: a 10-year experience by the U.S. food and drug administration. *J Clin Oncol* 2017;35:10009.
23 Hutchins LF, Unger JM, Crowley JJ, *et al*. Underrepresentation of patients 65 years of age or older in cancer-treatment trials. *N Engl J Med* 1999;341:2061–7.
24 Unger JM, Crowley JJ, Coltman CA, *et al*. Accrual patterns of the Southwest Oncology Group (SWOG) by sex, race/ethnicity, and age: updated and expanded analyses. *J Clin Oncol* 2004;22:6014.
25 The World Bank Group. Available: https://blogs.worldbank.org/opendata/new-world-bank-country-classifications-income-level-2022-2023 [Accessed 09 Sep 2023].
26 Heneghan C, Blacklock C, Perera R, *et al*. Evidence for non-communicable diseases: analysis of cochrane reviews and randomised trials by World Bank classification. *BMJ Open* 2013;3:e003298.
27 Noronha V, Rao A, Gattani S, *et al*. Impact of the geriatric assessment on cancer-directed systemic therapy in older Indian persons with cancer: an observational study. *Cancer Res Stat Treat* 2022;5:673.
28 Noronha V, Ramaswamy A, Dhekle R, *et al*. Initial experience of a geriatric oncology clinic in a tertiary cancer center in India. *Cancer Res Stat Treat* 2020;3:208.
29 Soto-Perez-de-Celis E, Li D, Yuan Y, *et al*. Functional versus chronological age: geriatric assessments to guide decision making in older patients with cancer. *Lancet Oncol* 2018;19:e305–16.
30 Sedrak MS, Freedman RA, Cohen HJ, *et al*. Older adult participation in cancer clinical trials: a systematic review of barriers and interventions. *CA A Cancer J Clinicians* 2021;71:78–92.
31 Bertagnolli MM, Singh H. Treatment of older adults with cancer - addressing gaps in evidence. *N Engl J Med* 2021;385:1062–5.