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Older cancer patients in cancer clinical trials are underrepresented. Systematic literature review of almost 5000 meta- and pooled analyses of phase III randomized trials of survival from breast, prostate and lung cancer

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ABSTRACT

Background: Older people represent increasing proportions of the population with cancer. To understand the representivity of cancer treatments in older people, we performed a systematic literature review using PRISMA guidelines of the age distribution of clinical trial participants for three leading cancer types, namely breast, prostate, and lung.
Methods: We used PubMed to identify articles detailing meta or pooled-analyses of phase III, randomised controlled trials (RCTs) of survival for breast, prostate and lung cancer, published ≤5 years from 2016. We compared the age distribution of participants to that of these cancers for "More developed regions".
Results: 4993 potential papers were identified, but only three papers on breast cancer, three on lung cancer, and none on prostate cancer presented the age distribution of their participants. Except for one paper of breast cancer, participants ≥70 years in all other papers were underrepresented.
Conclusions: We recommend the age distribution of patients be clearly reported in all clinical trials, as per guidelines. Clinical trials ought to be more representative of the populations most affected by the disease for which treatments are being tested. This should lead to better knowledge of effectiveness of treatments and better translation of trial results to optimal care of older cancer patients.

1. Introduction

In a recent report on global health and ageing [1], the number of people aged 65 or older is likely to increase 3-fold, from about 0.5 million in 2010 to 1.5 billion in 2050 [1].

This pattern in population is occurring in both high and low income countries around the world, and is projected to continue due to increasing life expectancy [2,3]. Such trends will undoubtedly result in an increased demand on the health system in all countries especially due to non-communicable disease such as cancer [1]. It has long been recognized that cancer incidence will increase dramatically over the next 50 years, especially among the elderly [3].

Currently, in developed countries, about 6 out of 10 incident cancers occur over an arbitrary cut-off of old age being 65 years [2]. With the number of incident cancers expected to rise and the greatest number being in older populations, the relative effectiveness of both current and evolving cancer treatments for this population needs to be better understood.

While cancer mortality has decreased in most developed countries over the past few decades, cancer survival continues to worsen with increased age. For example, in Australia, 5-year relative survival decreases noticeably after 60 years of age from just over 70% to less than 40% at age 80 and beyond [4].

Age alone is not used to limit access to cancer treatment. For example in Australia, this would be contrary to the Age Discrimination Act [5]. In practice, treatment decisions are made according to often-perceived likely risk-to-benefit ratio regarding the ability to tolerate treatment, side effects, co-morbidities and the quality of remaining life [6]. In such circumstances, it is critical for good decision making to have reliable age-relevant data from clinical trials to inform optimal care.

It is well recognised that elderly populations are underrepresented in cancer clinical trials. In an attempt to quantify this underrepresentation, we performed a systematic literature review of the age distribution of pooled or meta analyses of cancer clinical trial participants for three leading cancer types namely breast, prostate and lung.

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For illustrative purposes, we compared the age distribution of trial participants to a "More developed region" age/cancer distribution because all the relevant studies mostly arose in those regions (see below). We chose meta- or pooled analyses because these are likely to be the first to attract attention of policy makers.

2. Methods

We followed the published PRISMA 2009 guidelines [7]. Our review was limited to papers published within the past 5 years from May 2016, obtained via a PubMed search. Inclusion criteria included a language restriction to papers in English; and a study type of either meta-analyses or pooled analyses of phase III randomized controlled trials (RCT) only of cancer-specific treatments with a primary or secondary outcome of overall-survival (OS). Search was restricted to papers on breast, lung and prostate cancer, the three leading cancer types.

2.1. Literature search

Online PubMed searches were undertaken to identify relevant meta-analyses or pooled-analyses for each cancer type individually. Searches were conducted using PubMed up to May 2016. Search term used were "breast cancer treatment", or "prostate cancer treatment" or "lung cancer treatment" using the filters "clinical trials, phase III," "randomized controlled trial," "meta-analysis," and restricted to "human" subjects with a publication date within the "past 5-years".

2.2. Methods of study selection, quality assessment and data extraction

One reviewer (CD) inspected titles and abstracts of articles identified by PubMed searches and reviewed full-text versions when articles appeared potentially relevant. Inconsistencies were reviewed by CD and FS.

Data were extracted from each study that met all inclusion criteria and included sufficient information on the age distribution of its participants, paying special attention to reports of age distributions in participants above 65 years. Studies which only included the mean or range age of participants, but were otherwise relevant were excluded as were studies that included age distribution information in person-years. In cases where age distributions were provided in different groupings, (i.e., ages 45–55 versus 40–50), numbers were halved and each half were placed into corresponding age groups. It was practically difficult to ascertain 'representative' age/cancer distributions for each population reported, (and the populations represented in each of the meta or pooled analyses) but the vast majority of trials were conducted in developed countries. For this reason the age-specific incidence rates for breast, prostate and lung cancers were taken from the World Health Organization's (WHO) International Agency on Research for Cancer (IARC) GLOBOCAN's "More developed regions" [8]. Given the crude nature of this comparison, we performed no statistical tests.

3. Results

Literature searches yielded a total of 4993 references (Table 1). These results underwent a title/abstract screening which identified a total of 291 potentially relevant articles to be reviewed in full-text. After performing full-text assessments of articles, a total of six meta-analyses across the three cancer types had sufficient information on age distribution of participants to be included. Of these, three articles detailing breast cancer treatments and three detailing lung cancer treatments provided sufficient age distribution data for analysis; no relevant prostate cancer articles included sufficient age data for our analyses. A list of excluded studies is available on request (see Table 1 for numbers of articles excluded in each round of screening).

Meta- and pooled analyses were all conducted in European centres, drawing data mainly from a range of developed countries. In total, the meta-analyses included in our review contained data on 110,224 individuals. Studies explored a range of treatment methods such as chemotherapy, radiotherapy, and other drug therapy. All three breast cancer treatment articles included in our analysis were conducted by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) [9–11] and two of the three lung cancer treatment meta-analyses were conducted by the non-small-cell lung cancer (NSCLC) Meta-analysis Collaborative Group [12–14]. As each study detailed different treatment types the samples described in each paper were each considered independent.

3.1. Breast cancer

Three meta-analyses were identified and used in the current review [9–11]. Comparing these age distributions to the "More developed regions" age-specific incidence rates suggests that participants < 45, and 45–54 are over-represented in two of the three analyses (ranging from 15 to 20%), participants ages 55–69 were under-represented (two of the three breast cancer meta-analyses 10–12%). Participants aged ≥70 were consistently under-represented in all three meta-analyses in the region of 12–28% less than expected. The extent of under and over representation of these age groups in the included meta-analyses are depicted in Fig. 1 and described numerically, by proportion, in Table 2.

3.2. Prostate cancer

No meta- or pooled analyses pertaining to prostate cancer treatment clinical trials provided sufficient age information for inclusion in our review.

3.3. Lung cancer

Findings from the comparison of age-specific lung cancer incidence and age-groups defined and included in the studies included in our review [12–14] suggest an even greater disparity among age of participants included in clinical trials compared to the age groups most highly affected by lung cancer. Participants aged < 60, and between the ages 60–69 were consistently over-represented in all three lung cancer meta-analyses that were included in our review (11%-25%). In addition, patients ≥70, the age group at highest risk for developing lung cancer, were consistently under-represented across the three meta-analyses, between 20 and 35%, to what would be expected from the "background distribution" of this cancer type. The extent of under and over representation of these age groups in the included pooled or meta-

Table 1
Tabulation of literature searches and inclusion based on PRISMA flow-diagram. [7].

Cancer Type	Records identified through database searching	Records after duplicates removed	Records screened	Records excluded	Full-text articles assessed for eligibility	Full-text articles excluded, with reasons	Studies included in qualitative synthesis	Studies included in quantitative synthesis (meta-analysis)
Breast	2356	2356	2356	2243	113	110	3	3
Prostate	1089	1089	1089	1048	41	41	0	0
Lung	1548	1548	1548	1411	137	134	3	3