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Socioeconomic Differences in Referral to Phase I Cancer Clinical Trials: A Danish Matched Cancer Case-Control Study

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PURPOSE In this nationwide registry study, we investigated socioeconomic and structural patterns in referral to phase I cancer trials in a case-control study design.

METHODS Personal identification numbers on all Danish patients referred to the Danish Phase I Unit at Rigshospitalet from 2005 to 2016, and a control group matched on age, sex, type of cancer, year of diagnosis, and time from diagnosis to referral ensured individual-level linkage between several registries. We examined the association between nonclinical factors—indicators of socioeconomic position and distance to the Phase I Unit—and referral using a conditional logistic regression analysis adjusted for several clinical factors. Association between nonclinical factors and enrollment once referred was examined with a Cox proportional hazards regression analysis in an historical cohort study design.

RESULTS Complete data were available for 1,026 (84%) of 1,220 referred patients. Significantly decreased odds for referral were identified for patients with long distance to the Phase I Unit compared with short distance (adjusted odds ratio [OR], 0.35; 95% CI, 0.30 to 0.41), for less education (less than 9 years) compared with more (more than 12 years; OR, 0.69; 95% CI, 0.56 to 0.91), and for belonging to the lowest income quintile compared with the highest (OR, 0.78; 95% CI, 0.62 to 0.97). Medium education (9 to 12 years) compared with more, being outside the workforce compared with being within, and living alone compared with living with a partner were also negatively associated with referral. Among patients referred, 252 enrolled in a trial. Nonclinical factors were not associated with enrollment.

CONCLUSION On the basis of individual long-term registry data from an unselected cohort, novel anticancer therapies seem to be tested on a socially selected group of patients with cancer.

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INTRODUCTION

Recruitment to clinical trials is crucial for the development of new cancer therapeutics. The purpose of phase I trials is to define the toxicity profile,¹ although advances in cancer genomics with the detection of biomarkers have further guided therapeutic strategies.² It is possible that the chance of benefitting from phase I trials for patients with cancer with advanced progressive disease has increased as a result of a personalized approach that is based on genomic expression.³

It is well known that differences in clinical and nonclinical factors are associated with the recruitment of patients to cancer trials. Selection into trials is attributable to higher recruitment rates of patients at younger age, men, non-Hispanic whites, patients with health insurance, high income, and residence in urban areas⁴⁻⁸; however, the literature on recruitment specifically to phase I cancer trials is limited. Studies

from the United States demonstrate that participants in phase I trials are well educated and have high income.⁹⁻¹¹ Although these studies were conducted without a comparison group, results suggest that patients with higher socioeconomic position (SEP) are over-represented in phase I trials.

To explore whether improved strategies in phase I trials benefit a selected population, we investigated if, in Denmark, nonclinical factors are associated with differences in referral pattern to phase I trials, hypothesizing that low SEP and long distance to phase I unit were, in fact, significant barriers for referral, although not for enrollment once referred.

METHODS

Study Design

Our study investigated the association of nonclinical factors with referral as primary outcome in a matched case-control design. Cases were the unselected cohort

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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of all 1,220 patients referred since the establishment of the Danish Phase I Unit, from December 1, 2005, to April 30, 2016. We investigated the association of nonclinical factors with enrollment as a secondary outcome in an historical cohort design among referred patients only, with death as competing risk. SEP variables were selected to cover different aspects of social resources: ability to perceive and act on information (education), material resources (workforce and income), and social support (cohabitation and children living at home).^{12,13} Distance to the Phase I Unit was included, although it is not a typical SEP factor, as it represents a relevant structural challenge in a country with only one phase I unit. Covariables covered demographic and clinical factors that were considered to be likely to confound—age, sex, cancer type, and year of diagnosis—or mediate—presence or absence of metastases or physical or mental comorbidity—the association between nonclinical factors and referral.

Setting

In Denmark, the Phase I Unit at the Department of Oncology, Rigshospitalet, is the only dedicated unit established with the purpose of conducting phase I cancer trials on the basis of next-generation sequencing since 2013,¹⁴ whereas phase II and III trials are conducted at several departments nationwide. Patients from all over the country are referred by local hospital-based oncologists. No private oncologic services are offered to residents of the country.

Study Population

From the electronic patient administrative system at the hospital, we obtained baseline data on referral diagnosis, date of referral, and the national personal 10-digit identification number (PIN).

Danish Civil Registration System

Since 1968, all residents of Denmark have been recorded in the Danish Civil Registration System and assigned a PIN that encodes sex and date of birth. The PIN enables the linkage between all national registries and administrative databases.^{15,16} From this registry, we obtained data on vital status, migrations, cohabitation (living alone or with a partner), children living at home (yes or no), and distance to the Phase I Unit for the year of index date (referral/matching). Distance to the Phase I Unit followed the five administrative geographic regions of Denmark with categorization as short distance (same region as the Unit, driving distances within 30 miles), medium (neighboring region, distances within 120 miles), or far (remaining three regions, distances within 330 miles).

Danish Cancer Registry

Since 1943, detailed information on all patients with cancer has been registered in the Danish Cancer Registry (DCR), the oldest nationwide, population-based cancer registry in the world.¹⁷ From DCR, we obtained information on the type of cancer, date of diagnosis, presence or absence of

metastases, and the number of other cancer diseases at the time of diagnosis (zero, one, or two or more). On the basis of International Statistical Classification of Diseases, Tenth Revision (ICD-10) codes, we created 14 diagnostic groups for adjustments in analyses—buccal cavity and pharynx (ICD-10 C00-C14), digestive organs (C15-C26), respiratory system and intrathoracic organs (C30-C39), bones and articular cartilage (C40-C41), skin (C43, C460), mesothelium and connective tissue (C45-C49), breast (C50), female genitals (C51-C58), male genitals (C60-C63), urinary tract (C64-C68), CNS (C69-C72, C751-C752), endocrine glands (C73-C74, C750, C754-759), ill-defined cancer (C76-C80), and lymphatic and hematopoietic tissue (C81-C96).

Statistics Denmark

Since 1850, Statistics Denmark has produced statistics on all people resident in Denmark. The comprehensive collection of data now includes such information as education (since 1974¹⁷) and income (since 1970¹⁸). From here, we obtained information on the following: highest attained educational level, categorized as less education (less than 9 years, elementary and junior high school), medium education (9 to 12 years, high school or vocational education), and more education (more than 12 years, higher education); affiliation to work market categorized as within (employed, unemployed, leave, or reduced work ability) and outside (early retirement as a result of disability, pensioners, and students); and disposable income, which was divided into quintiles on the basis of yearly income after taxes compared with the Danish population of the same age, sex, and year.

Danish National Patient Registry

Since 1978, the Danish National Patient Registry has stored nationwide information on patients' hospital admissions: date of admission, diagnosis, treatments, and operations on the basis of on patients' somatic admissions. In 1994, outpatient visits and ICD-10 codes were added, and psychiatric admissions were included beginning in 1995.^{19,20} Comorbidity was obtained from this registry and measured as the Charlson comorbidity index²¹ on the basis of diagnoses from somatic hospitalizations or outpatient contacts in a 10-year period before the index date (score of 0, 1, or 2 or more).

Danish National Prescription Registry

From 1995, all prescribed medication dispensed at Danish pharmacies has been registered with detailed information on type, strength, and number of units.^{22,23} We obtained data on psychological burden, measured as at least two prescriptions or more for either antidepressants (N06A) or anxiolytics (N05BA) for a 10-year period up to the index date (yes or no).

Selection of Controls

For each patient-case, we identified all matching controls on age (year of birth \pm 3 years), sex, type of cancer

(diagnostic groups on the basis of ICD-10 coding), and year of diagnosis (± 1 year) from the DCR. Furthermore, we ensured that eligible controls were alive at the date of referral of the patient. Patients could be controls for others before their own referral, and the same person could act as a control for several patients.

Congruence between patients' referral diagnosis and the diagnosis in the DCR was necessary for the extraction of clinical data. We excluded 77 patients who lacked consistency between the two diagnoses or for whom there was no registry diagnosis. Five patients who were referred with an advanced nonmelanoma skin cancer were likewise excluded as the rarity of the disease presentation made these patients incomparable with those with a non-malignant disease presentation. Seven patients who were not living in Denmark at the time of diagnosis were also excluded. No matching controls existed for 24 patients. This led to the exclusion of the rarest cases of cancer, leaving a total of 1,107 patients (91%) who were eligible for matching.

We matched patients individually, allowing for an indefinite number of controls to avoid the exclusion of rare cases. The total number of controls was thus 241,226, with a median of 87 (range one to 2,805) controls per case.

Complete data on all variables and covariables were available for 1,026 patients, thereby excluding 81 patients (7%; Fig 1).

Statistical Analysis

To evaluate the primary outcome, we estimated odds ratios (ORs) with 95% CIs for referral for each nonclinical factor

separately using conditional logistic regression, thereby accounting for the different numbers of controls. We studied three models: an unadjusted Model 0, which included no covariables, except the exposure of interest; Model 1, which also included mediators (the presence or absence of metastases, number of cancers, comorbidity, and psychological burden); and Model 2, which also included nonclinical factors. Furthermore, we tested for the effect modification by sex, age group, presence or absence of metastases, year of referral, and distance to the Phase I Unit, respectively, using likelihood ratio tests. In the presence of a significant effect modification, we conducted stratified analyses to assess ORs for individual groups.

For the secondary outcome, we applied Cox proportional hazards regression models to estimate hazard ratios (HRs) with 95% CIs for enrollment among referred patients for each nonclinical factor separately. The start of follow-up was date of referral. The end of follow-up was defined as either the date of inclusion in the first trial, the date of death, or 2 years after referral, whichever came first. We studied three models: an unadjusted Model 0; a Model 1 adjusted for confounders (age and year of referral modulated with a polynomial spline, and sex); and a Model 2 adjusted for possible mediators (number of cancers, presence or absence of metastases, comorbidity, and psychological burden). We tested the proportional hazard assumption on the basis of Schoenfeld residuals. Violations were found for the variable diagnostic groups and analyses were thus stratified on this variable. Furthermore, violations were found for the variables, children living at home and distance to the Phase I Unit, and we consequently divided the time

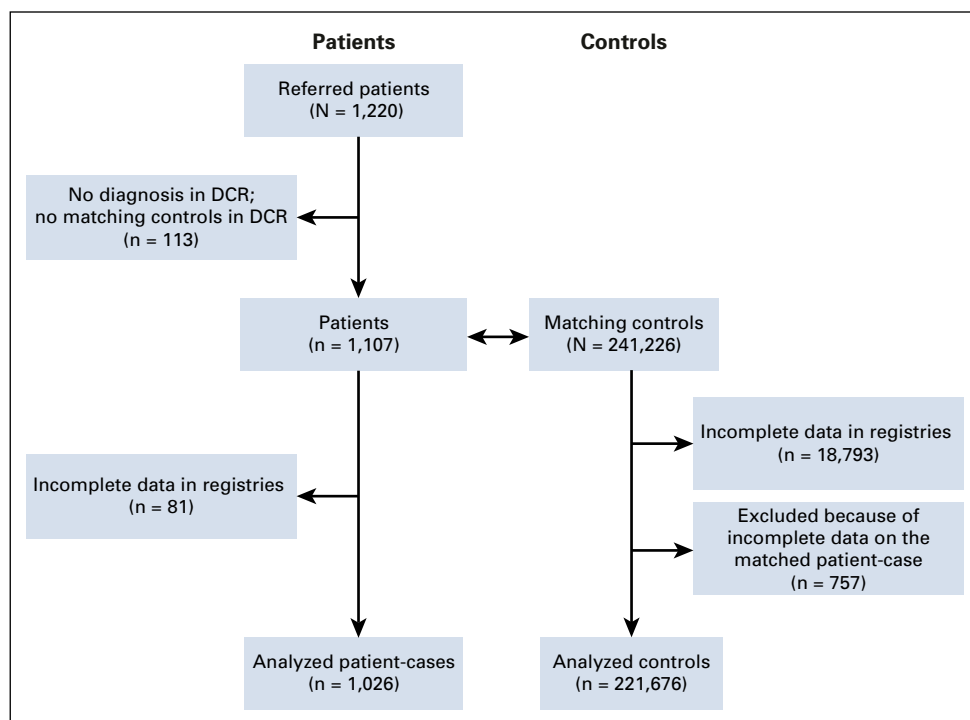


FIG 1. Flow diagram of the study population of patients and controls. Matching criteria included the following: age, sex, type of cancer, year of diagnosis, and days from diagnosis to index date (referral/matching). DCR, Danish Cancer Registry.

TABLE 1. Characteristics of Patients Referred to the Danish Phase I Unit and Matching Controls, Denmark, 2005 to 2016 (n = 1,107 and n = 241,226, respectively)

Characteristic	Patients	Controls
No. of patients	1,107 (100)	241,226 (100)
Sex		
Male	603 (54)	148,853 (62)
Female	504 (46)	92,373 (38)
Age, years		
Median (IQR)	59 (51-65)	64 (59-68)
< 45	165 (15)	9,991 (4)
45-64	655 (59)	131,330 (54)
≥ 65	287 (26)	99,905 (41)
Year of diagnosis		
≤ 2000	45 (4)	6,554 (3)
2001-2005	215 (19)	43,745 (18)
2006-2010	452 (41)	103,955 (43)
2011-2016	395 (36)	86,972 (36)
Time from diagnosis to index date, years		
Median (IQR)	2.01 (1.08-3.63)	2.41 (1.28-4.08)
< 1	255 (23)	47,171 (20)
1-2	484 (44)	101,186 (42)
3-4	191 (17)	47,458 (20)
≥ 5	177 (16)	45,411 (19)
No. of other tumors		
0	938 (85)	199,252 (83)
1	146 (13)	36,201 (15)
2	23 (2)	5,773 (2)
Distant metastases		
M0	471 (43)	166,967 (69)
M1	478 (43)	28,723 (12)
Mx	102 (9)	41,903 (17)
Missing information	56 (5)	3,633 (2)
Prescription		
No	761 (69)	172,646 (72)
Yes	346 (31)	68,580 (28)
Charlson comorbidity index		
0	816 (74)	164,274 (68)
1	218 (20)	49,944 (21)
2	73 (7)	27,008 (11)

NOTE. Data are given as No. (%), unless otherwise noted. The distribution for each variable is not comparable between patients and controls because of the various number of controls per patient. The number of tumors includes nonmalignant tumors. The index date is the date of referral (patients) or matching (controls). Prescriptions are for a 10-year period up to the index date.

Abbreviation: IQR, interquartile range.

scale at 30 days (30 days or less and more than 30 days) on the basis of the visual inspection of the residuals. Analyses were based on 1,026 complete cases (84% of 1,220) and 221,676 controls (92%) and carried out using R software version 3.4.2²⁴ and relevant packages.²⁵⁻³²

Ethics and Data Protection

This registry study was conducted with approval from The Danish Data Protection Agency (file number 2015-41-4445) and The Danish Patient Safety Authority (file number 3-3013-1400/1).

Reporting of the study follows the Strengthening the Reporting of Observational Studies in Epidemiology statement.³³

RESULTS

Descriptive Statistics

Patient characteristics according to demographic and clinical covariables are listed in [Table 1](#) and [Appendix Figure A1](#) (online only) for the distribution of cancer types.

Primary Outcome

Long distance compared with short distance to the Phase I Unit significantly decreased the likelihood for referral (Model 2: OR, 0.35; 95% CI, 0.30 to 0.41), as did less education compared with more (OR, 0.69; 95% CI, 0.56 to 0.84), as well as belonging to the lowest income group compared with the highest (OR, 0.78; 95% CI, 0.62 to 0.97). Furthermore, ORs for referral were significantly decreased for patients outside compared with those within the workforce (OR, 0.76; 95% CI, 0.63 to 0.91) and for patients with medium education compared with more education (OR, 0.77; 95% CI, 0.67 to 0.90), as well as for individuals living alone compared with living with a partner (OR, 0.83; 95% CI, 0.72 to 0.97; [Fig 2](#)). Adjustments for covariables did not change the significance level and only resulted in slight changes in estimates in Model 1, indicating that the mediators explained only part of the effect of the nonclinical factors ([Fig 2](#)). Results of effect modification tests and stratified analyses are listed in [Appendix Tables A1-A7](#) (online only).

Secondary Outcomes

A total of 252 patients who were referred to the Phase I Unit were subsequently enrolled in at least one trial, among whom data were complete for 197 (78%). The Cox proportional hazards regression analysis demonstrated that once the patients had been referred, nonclinical factors were not associated with the hazard of enrollment. Although they were based on a small number of events, time-split analyses suggested variations over time. Therefore, no children living at home compared with children living at home increased the hazard of enrollment within the first 30 days after referral (HR, 2.02; 95% CI, 1.07 to 3.82); however, this variable more than 30 days after referral did not affect referral. Furthermore, long distance compared

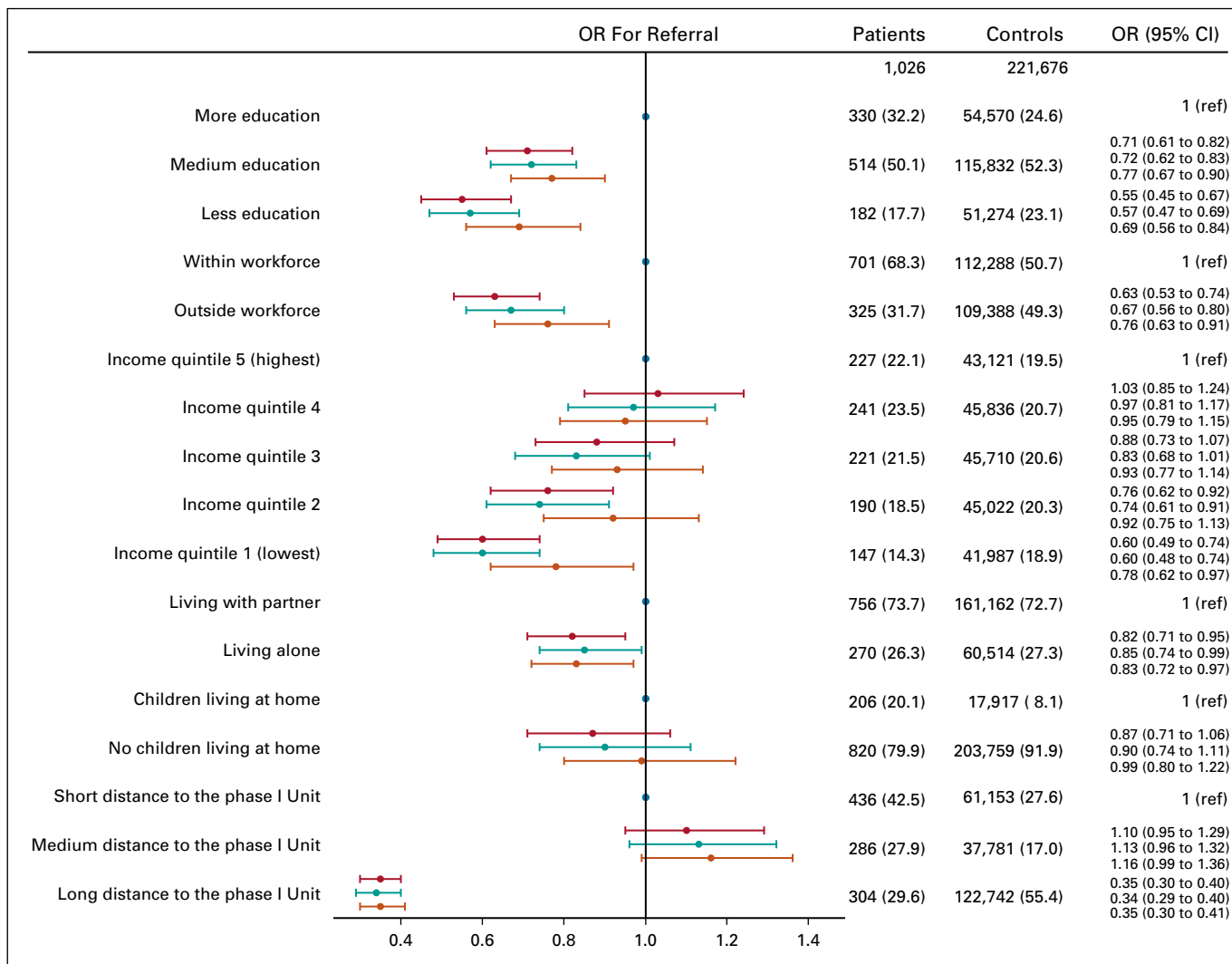


FIG 2. Odds ratios (ORs) with 95% CIs for referral to the Danish Phase I Unit ($n = 1,026$ referred patients and $n = 221,676$ controls), Denmark, 2005 to 2016, by socioeconomic characteristics. Light blue, reference; red, Model 0, unadjusted model, confounders included by method; teal, Model 1, adjusted for the number of cancers and presence or absence of metastases at diagnosis, as well as for psychological burden and comorbidity 10 years before referral (mediators); dark orange, Model 2, adjusted for mediators and mutually for the socioeconomic position variables and distance to the Phase I Unit. Less education is defined as less than 9 years, elementary and junior high school. Medium education is defined as 9 to 12 years, high school or vocational education. More education is defined as more than 12 years, higher education. Ref, reference.

with short distance from the Phase I Unit decreased time to enrollment within the first 30 days after referral (HR, 0.55; 95% CI, 0.31 to 0.95), whereas time to enrollment was increased more than 30 days after referral (HR, 1.86; 95% CI, 1.15 to 3.01; Fig 3). Results could not be explained by mediators (Appendix Table A8, online only).

DISCUSSION

Across all nonclinical factors analyzed, with the exception of children living at home, we observed a consistent pattern of lower odds for referral to the national Phase I Unit with low SEP and long distance to the Phase I Unit. The likelihood for enrollment once referred seemed to differ over time after referral for the variables, children living at home

and distance to the Phase I Unit. Because of the small numbers of events as a consequence of the time split, firm conclusions cannot be reached with regard to the effect of these variables. For the remaining variables, we did not find that nonclinical factors influenced enrollment.

The main strength of our study is the ability to compare the entire, unselected, nationwide cohort of previously referred patients with a closely matched control group of patients with cancer on a number of specific individual data. Inclusion of several demographic and clinical factors reduced the likelihood that our results can be explained by patient characteristics. Our analyses were based on comprehensive long-term registry data with individual-level linkage between administrative registries established years before

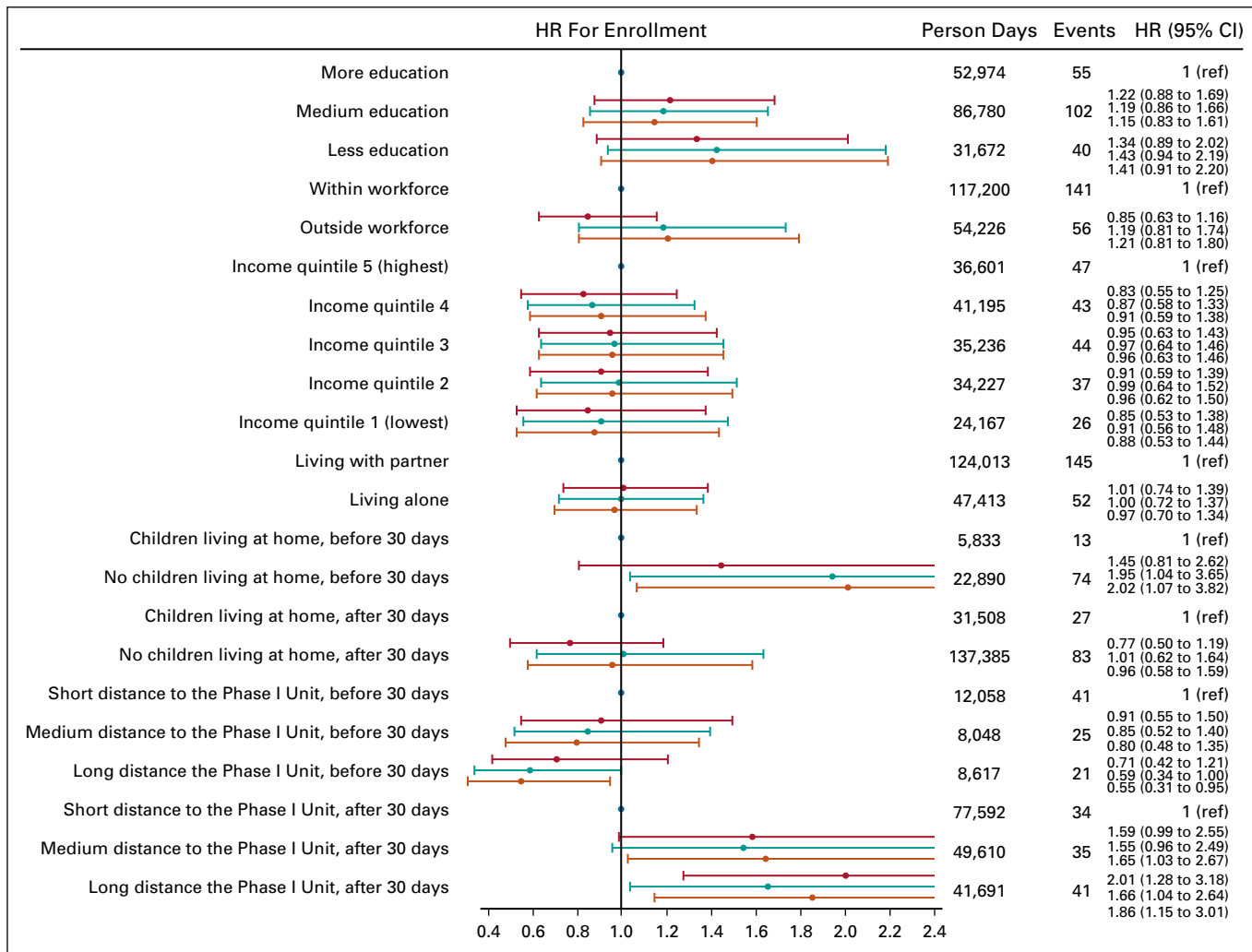


FIG 3. Hazard ratios (HRs) with 95% CIs for enrollment in phase I trials (n = 197 enrolled patients and n = 1,026 referred patients), Denmark, 2005 to 2016, by socioeconomic characteristics. Light blue, reference; red, Model 0, unadjusted analysis; teal, Model 1, adjusted for age, sex, and year of referral (confounders); dark orange, Model 2, adjusted for confounders and the number of cancers, cancer type, comorbidity, and psychological burden. Less education is defined as less than 9 years, elementary and junior high school. Medium education is defined as 9 to 12 years, high school or vocational education. More education is defined as more than 12 years, higher education. Without the time split, the estimate for no children living at home compared with children living at home was HR, 1.31 (95% CI, 0.86 to 1.98) and the estimate for distance to the Danish Phase I Unit was HR, 1.19 (95% CI, 0.84 to 1.68) for medium distance compared with short distance and HR, 1.08 (95% CI, 0.75 to 1.55) for long distance compared with short distance. Ref, reference.

the conception of our hypothesis and were thus independent of the hypothesis being tested and free of the recall bias that could potentially compromise results that are based on self-reported data.

Results from registry data involve some limitations. We had to exclude 113 (9%) of 1,220 total patients before matching as there was no pattern in referral diagnosis for these patients, which was interpreted as unsystematic missing data. The remaining exclusion of 29 patients (2%) without matching controls was a result of rare cancer diseases, meaning that they were systematic and with potential influence on the generalizability of this study. Furthermore, as phase I trials include patients with an advanced cancer disease and Eastern Cooperative Oncology Group

performance status (PS)³⁴ of 0 to 1, the presence or absence of metastases and PS for patients at referral were known. Controls may not have experienced a relapse, but, conversely, they could have had worse PS than patients at the index date. We addressed this by ensuring that controls were still alive at the time of the referral of the appertaining case.

Our findings of differences in access to health care services are in line with a registry study from the United Kingdom of 430 patients who were referred to a National Healthcare Service phase I trial compared with the general cancer population.³⁵ On the basis of a deprivation index, the most deprived patients had roughly one half the chance (OR, 0.53; 95% CI, 0.38 to 0.74) compared with the least

deprived patients of being referred to a phase I trial. This study identifies referral as the crucial point for a selection that is based on SEP. Once referred, retrospective chart reviews of 667 Canadian patients and 167 patients from the United Kingdom did, in fact, suggest that the obstacles for trial entry were related to clinical factors—protocol criteria and individual clinical factors.^{36,37} On the basis of our findings, selection by nonclinical factors seems to occur at referral.

Our results could not be explained by clinical covariables. Missing information on PS for controls could cause residual mediation. An association between low PS and more education, as has been demonstrated among 6,234 patients with non-Hodgkin lymphoma,³⁸ would cause an overestimation of the association between nonclinical factors and referral if controls had worse PS than did patient-cases.

Distance to the Phase I Unit may reflect both structural challenges and differences in SEP across regions. In testing for effect modification, distance did not affect the impact of most SEP variables. Distance to the Phase I Unit was identified as a reason for declining entry in a trial in a study of 267 US patients, of whom 37 refused trial offers.³⁹ However, in a retrospective chart review of 365 patients and in a questionnaire survey of 106 patients, distance to the hospital did not affect trial entry once patients had been referred.⁴⁰ This suggests that considerations of travel time take place before referral. Although cautious interpretation should be made because of the low number of events, we found that long distance promotes enrollment more than 30 days after enrollment. Given the risk of rapid deterioration, this finding may be explained by better health among referred patients with long distance to the Phase I Unit. This is in line with an historical cohort study of 110 patients who participated in phase II trials in which patients who lived more than 15 miles from the hospital had one third the hazard of death.⁴¹

The presented association between nonclinical factors and referral is assumed to be mediated by factors related to the referring oncologists and patients (Appendix Fig A2, online only). Referring oncologists may have contributed to the skewed selection. In a cross-sectional study from the United States that included 405 women with breast cancer, young age, being non-Hispanic white, additional education, and higher income were associated with better communication between physician and patient,⁴² although methodologic limitations do not allow solid conclusions. Whether our findings reflect actual disparities⁴³ cannot be determined within this study design. As a consequence, improved strategies in phase I trials do not benefit an unselected population.

Because of the exclusion of the rarest cases—2% of the entire patient population—as a result of the lack of matching controls, our results cannot be generalized to the complete population of patients referred to a phase I unit. The current study demonstrates differences in referral according to SEP and distance to a phase I unit in a country with universal and publicly funded health care. As such selection may be even more pronounced when health care is based on governmental or private insurance or there is no insurance at all, we expect our results to be relevant also in countries with these health care conditions.

In conclusion, despite every Danish resident's access to universal, tax-funded, income-independent health care, low SEP and long distance to the Danish Phase I Unit is a barrier for referral. We find it important to draw attention to the fact that the development of new anticancer therapies seems to rely on a socially selected group of patients with cancer, not only in terms of clinical factors but also social characteristics. Our findings are of relevance in relation to drug development, especially when applying findings from experimental trials to the entire population of patients with cancer.

AFFILIATIONS

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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Manuscript writing: All authors

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APPENDIX

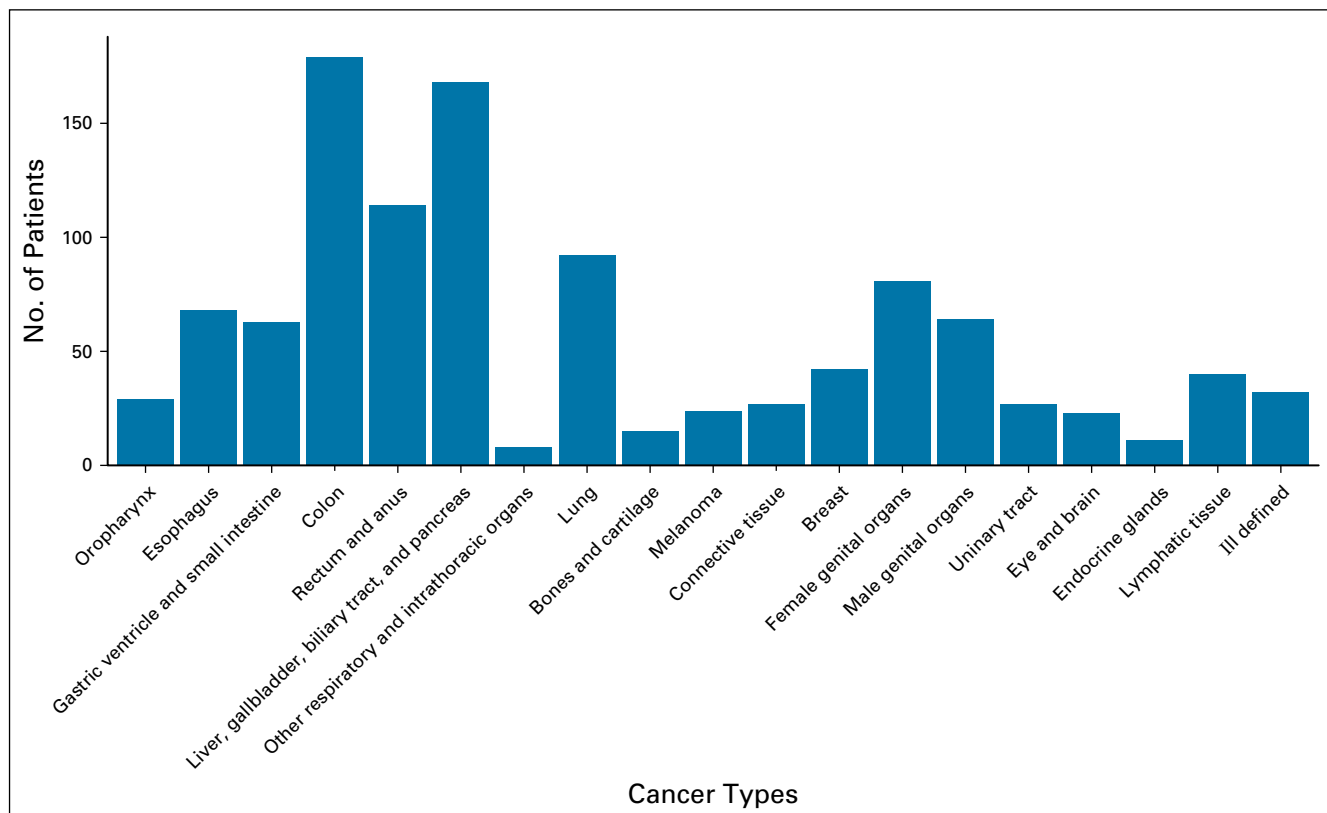


FIG A1. Distribution of cancer types among patients who were referred to the Danish Phase I Unit (n = 1,107), Denmark, 2005 to 2016.

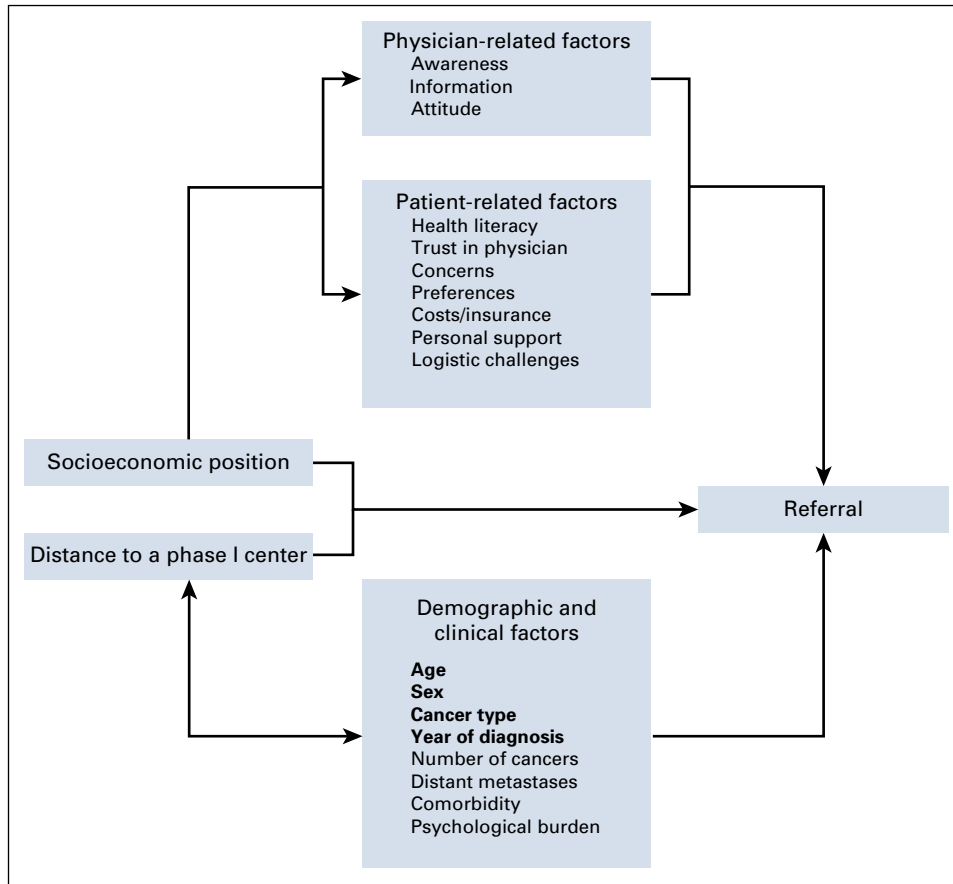


FIG A2. Hypothetical model of relationships between socioeconomic position, demographic and clinical factors, and nonclinical factors—physician related and patient related—on referral to a phase I unit. Matching variables are written in bold.

TABLE A1. Individual Testing of the Effect of Each Mediator From Model 1 on ORs With 95% CIs For Referral to the Phase I Unit, Denmark, 2005 to 2016, by Socioeconomic Characteristics (n = 1,026 referred patients and n = 221,676 controls)

Characteristic	Patients, No. (%)	Controls, No. (%)	Unadjusted Analysis, OR (95% CI)	No. of Cancers, OR (95% CI)	Distant Metastases, OR (95% CI)	Psychological Burden, OR (95% CI)	Comorbidity, OR (95% CI)
Education level							
More	330 (32.2)	56,628 (24.6)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium	514 (50.1)	119,939 (52.2)	0.71 (0.61 to 0.82)	0.71 (0.61 to 0.82)	0.71 (0.62 to 0.82)	0.71 (0.61 to 0.82)	0.72 (0.63 to 0.83)
Less	182 (17.7)	53,221 (23.2)	0.55 (0.45 to 0.67)	0.55 (0.45 to 0.67)	0.56 (0.46 to 0.67)	0.55 (0.45 to 0.67)	0.57 (0.47 to 0.69)
Workforce participation							
Within the workforce	701 (68.3)	115,856 (50.4)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Outside the workforce	325 (31.7)	113,932 (49.6)	0.63 (0.53 to 0.74)	0.63 (0.53 to 0.74)	0.65 (0.54 to 0.77)	0.62 (0.53 to 0.74)	0.65 (0.55 to 0.78)
Income quartile							
5 (highest)	227 (22.1)	44,726 (19.5)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
4	241 (23.5)	47,695 (20.8)	1.03 (0.85 to 1.24)	1.03 (0.86 to 1.24)	0.98 (0.81 to 1.18)	1.03 (0.85 to 1.24)	1.02 (0.85 to 1.23)
3	221 (21.5)	47,469 (20.7)	0.88 (0.73 to 1.07)	0.88 (0.73 to 1.07)	0.84 (0.69 to 1.01)	0.88 (0.73 to 1.07)	0.87 (0.72 to 1.06)
2	190 (18.5)	46,563 (20.3)	0.76 (0.62 to 0.92)	0.76 (0.62 to 0.92)	0.74 (0.60 to 0.90)	0.76 (0.62 to 0.92)	0.76 (0.63 to 0.93)
1 (lowest)	147 (14.3)	43,335 (18.9)	0.60 (0.49 to 0.74)	0.60 (0.49 to 0.74)	0.59 (0.47 to 0.73)	0.60 (0.49 to 0.74)	0.61 (0.50 to 0.76)
Living with a partner							
Yes	756 (73.7)	167,615 (72.9)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
No (living alone)	270 (26.3)	62,173 (27.1)	0.82 (0.71 to 0.95)	0.82 (0.71 to 0.95)	0.84 (0.72 to 0.97)	0.82 (0.71 to 0.95)	0.84 (0.73 to 0.97)
Children living at home							
Yes	206 (20.1)	18,455 (8.0)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
No	820 (79.9)	211,333 (92.0)	0.87 (0.71 to 1.06)	0.87 (0.71 to 1.06)	0.89 (0.73 to 1.09)	0.87 (0.71 to 1.06)	0.88 (0.72 to 1.07)
Distance to the phase I unit							
Short	436 (42.5)	63,476 (27.6)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium	286 (27.9)	39,135 (17.0)	1.10 (0.95 to 1.29)	1.10 (0.95 to 1.29)	1.13 (0.97 to 1.32)	1.10 (0.95 to 1.29)	1.10 (0.95 to 1.29)
Long	304 (29.6)	127,177 (55.3)	0.35 (0.30 to 0.40)	0.35 (0.30 to 0.40)	0.35 (0.30 to 0.40)	0.35 (0.30 to 0.40)	0.34 (0.29 to 0.40)

NOTE. Less education is defined as less than 9 years, elementary and junior high school. Medium education is defined as 9 to 12 years, high school or vocational education. More education is defined as more than 12 years, higher education.

Abbreviations: OR, odds ratio; ref, reference.

TABLE A2. ORs With 95% CIs For Referral to the Phase I Unit, Denmark, 2005 to 2016, in a Subgroup Analysis of Distance to the Phase I Unit by Sex (n = 142,458 males and n = 88,356 females)

Distance to the Phase I Unit	Male, No. (%)	Male, OR (95% CI)	Female, No. (%)	Female, OR (95% CI)
Short	39,394 (27.7)	1 (ref)	24,518 (27.7)	1 (ref)
Medium	24,875 (17.5)	1.31 (1.06 to 1.62)	14,546 (16.5)	0.98 (0.77 to 1.25)
Long	78,189 (54.9)	0.31 (0.25 to 0.39)	49,292 (55.8)	0.40 (0.32 to 0.50)

Abbreviations: OR, odds ratio; ref, reference.

TABLE A3. ORs With 95% CIs For Referral to the Phase I Unit, Denmark, 2005 to 2016, in a Subgroup Analysis of Distance to the Phase I Unit by Age Categories (n = 9,536 patients < 45 years, n = 126,057 age 45 to 64 years, and n = 95,221 ≥ 65 years of age)

Distance to the Phase I Unit	Age < 45 Years, No. (%)	Age < 45 Years, OR (95% CI)	Age 45-64 Years, No. (%)	Age 45-64 Years, OR (95% CI)	Age ≥ 65 Years, No. (%)	Age ≥ 65 Years, OR (95% CI)
Short	3,071 (32.2)	1 (ref)	34,777 (27.6)	1 (ref)	26,064 (27.4)	1 (ref)
Medium	1,396 (14.6)	1.06 (0.62 to 1.81)	21,304 (16.9)	1.29 (1.06 to 1.58)	16,721 (17.6)	0.89 (0.66 to 1.21)
Long	5,069 (53.2)	0.67 (0.44 to 1.01)	69,976 (55.5)	0.37 (0.30 to 0.45)	52,436 (55.1)	0.21 (0.15 to 0.30)

Abbreviations: OR, odds ratio; ref, reference.

TABLE A4. ORs With 95% CIs For Referral to the Phase I Unit, Denmark, 2005 to 2016, in a Subgroup Analysis of Income by Referral Year (n = 141,544 patients referred before 2014 and n = 89,270 referred from 2014 to 2016)

Income Quintile	Referral Before 2014, No. (%)	Referral Before 2014, OR (95% CI)	Referral Since 2014, No. (%)	Referral Since 2014, OR (95% CI)
5 (highest)	27,910 (19.7)	1 (ref)	17,043 (19.1)	1 (ref)
4	29,202 (20.6)	0.94 (0.73 to 1.20)	18,734 (21.0)	0.98 (0.72 to 1.31)
3	29,089 (20.6)	1.00 (0.78 to 1.29)	18,601 (20.8)	0.85 (0.62 to 1.16)
2	28,656 (20.2)	1.15 (0.89 to 1.49)	18,097 (20.3)	0.61 (0.43 to 0.89)
1 (lowest)	26,687 (18.9)	0.84 (0.63 to 1.11)	16,795 (18.8)	0.70 (0.49 to 1.02)

Abbreviations: OR, odds ratio; ref, reference.

TABLE A5. ORs With 95% CIs For Referral to the Phase I Unit, Denmark, 2005 to 2016, in a Subgroup Analysis of Distance to the Phase I Unit by Referral Year (n = 141,544 patients referred before 2014 and n = 89,270 referred from 2014 to 2016)

Distance to the Phase I Unit	Referral Before 2014, No. (%)	Referral Before 2014, OR (95% CI)	Referral Since 2014, No. (%)	Referral Since 2014, OR (95% CI)
Short	39,721 (28.1)	1 (ref)	24,191 (27.1)	1 (ref)
Medium	24,333 (17.2)	1.19 (0.99 to 1.44)	15,088 (16.9)	1.06 (0.79 to 1.42)
Long	77,490 (54.7)	0.23 (0.18 to 0.28)	49,991 (56.0)	0.64 (0.50 to 0.81)

Abbreviations: OR, odds ratio; ref, reference.

TABLE A6. ORs With 95% CIs For Referral to the Phase I Unit, Denmark, 2005 to 2016, in a Subgroup Analysis of Workforce by Distance to the Phase I Unit (n = 63,912 patients with short distance, n = 39,421 patients with medium distance, and n = 127,481 patients with long distance to Phase I Unit)

Workforce Participation	Short Distance to the Phase I Unit, No. (%)	Short Distance to the Phase I Unit, OR (95% CI)	Medium Distance to the Phase I Unit, No. (%)	Medium Distance to the Phase I Unit, OR (95% CI)	Long Distance to the Phase I Unit, No. (%)	Long Distance to the Phase I Unit, OR (95% CI)
Within the workforce	33,790 (52.9)	1 (ref)	19,177 (48.6)	1 (ref)	63,590 (49.9)	1 (ref)
Outside the workforce	30,122 (47.1)	0.73 (0.55 to 0.97)	20,244 (51.4)	0.83 (0.58 to 1.20)	63,891 (50.1)	0.70 (0.48 to 1.02)

Abbreviations: OR, odds ratio; ref, reference.

TABLE A7. Subgroup Analysis of ORs With 95% CIs For Referral to the Phase I Unit, Denmark, 2005 to 2016, by Children Living at Home (n = 63,912 patients with short distance, n = 39,421 patients with medium distance, and n = 127,481 patients with long distance to Phase I Unit)

Children Living at Home	Short Distance to the Phase I Unit, No. (%)	Short Distance to the Phase I Unit, OR (95% CI)	Medium Distance to the Phase I Unit, No. (%)	Medium Distance to the Phase I Unit, OR (95% CI)	Long Distance to the Phase I Unit, No. (%)	Long Distance to the Phase I Unit, OR (95% CI)
Yes	5,955 (9.3)	1 (ref)	2,429 (6.9)	1 (ref)	9,977 (7.8)	1 (ref)
No	57,957 (90.7)	1.53 (1.05 to 2.22)	36,692 (93.1)	0.76 (0.47 to 1.22)	117,504 (92.2)	0.76 (0.53 to 1.11)

Abbreviations: OR, odds ratio; ref, reference.

TABLE A8. Individual Testing of the Effect of Each Mediator From Model 2 on HRs With 95% CIs For Enrollment in a Phase I Trial, Denmark, 2005 to 2016, by Socioeconomic Characteristics (n = 252 enrolled patients and n = 10,726 referred patients)

Characteristic	Person Days, No.	No.	Event	Unadjusted Analysis	No. of Cancers, HR (95% CI)	Distant Metastases, HR (95% CI)	Psychological Burden, HR (95% CI)	Comorbidity, HR (95% CI)
Education level								
More	52,974	330	55	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium	86,780	514	102	1.22 (0.88 to 1.69)	1.17 (0.84 to 1.63)	1.17 (0.84 to 1.63)	1.20 (0.86 to 1.66)	1.19 (0.86 to 1.66)
Less	31,672	182	40	1.34 (0.89 to 2.02)	1.41 (0.92 to 2.16)	1.45 (0.94 to 2.25)	1.43 (0.93 to 2.18)	1.42 (0.92 to 2.18)
Workforce participation								
Within the workforce	117,200	701	141	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Outside the workforce	54,226	325	56	0.85 (0.63 to 1.16)	1.21 (0.82 to 1.79)	1.19 (0.81 to 1.76)	1.18 (0.81 to 1.74)	1.18 (0.80 to 1.73)
Income quintile								
5 (highest)	36,601	227	47	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
4	41,195	241	43	0.83 (0.55 to 1.25)	0.88 (0.58 to 1.33)	0.91 (0.60 to 1.39)	0.87 (0.57 to 1.32)	0.87 (0.58 to 1.32)
3	35,236	221	44	0.95 (0.63 to 1.43)	0.96 (0.63 to 1.45)	0.98 (0.64 to 1.50)	0.96 (0.63 to 1.45)	0.97 (0.64 to 1.46)
2	34,227	190	37	0.91 (0.59 to 1.39)	0.97 (0.63 to 1.51)	0.96 (0.62 to 1.50)	0.97 (0.63 to 1.51)	0.97 (0.63 to 1.51)
1 (lowest)	24,167	147	26	0.85 (0.53 to 1.38)	0.90 (0.56 to 1.46)	0.90 (0.55 to 1.47)	0.91 (0.56 to 1.47)	0.90 (0.56 to 1.47)
Living with a partner								
Yes	124,013	756	145	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
No (living alone)	47,413	270	52	1.01 (0.74 to 1.39)	1.01 (0.73 to 1.39)	0.95 (0.69 to 1.32)	0.99 (0.72 to 1.37)	0.99 (0.72 to 1.37)
Children living at home								
Yes, before 30 days	5,833	206	13	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
No, before 30 days	22,890	820	74	1.45 (0.81 to 2.62)	1.98 (1.06 to 3.71)	1.85 (0.99 to 3.47)	1.95 (1.04 to 3.64)	1.95 (1.04 to 3.66)
Yes, after 30 days	31,508	178	27	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
No, after 30 days	137,385	695	83	0.77 (0.50 to 1.19)	1.03 (0.63 to 1.67)	0.93 (0.57 to 1.52)	1.00 (0.62 to 1.63)	1.00 (0.62 to 1.63)
Distance to the Phase I Unit								
Short, before 30 days	12,058	436	41	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium, before 30 days	8,048	286	25	0.91 (0.55 to 1.50)	0.86 (0.52 to 1.42)	0.83 (0.50 to 1.37)	0.85 (0.52 to 1.40)	0.85 (0.52 to 1.40)
Long, before 30 days	8,617	304	21	0.71 (0.42 to 1.21)	0.59 (0.35 to 1.01)	0.58 (0.34 to 1.00)	0.58 (0.34 to 1.00)	0.59 (0.34 to 1.00)
Short, after 30 days	77,592	365	34	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Medium, after 30 days	49,610	246	35	1.59 (0.99 to 2.55)	1.57 (0.98 to 2.52)	1.51 (0.93 to 2.43)	1.56 (0.97 to 2.51)	1.55 (0.96 to 2.49)
Long, after 30 days	41,691	262	41	2.01 (1.28 to 3.18)	1.68 (1.05 to 2.67)	1.70 (1.06 to 2.74)	1.66 (1.04 to 2.64)	1.67 (1.05 to 2.65)

NOTE. Less education is defined as less than 9 years, elementary and junior high school. Medium education is defined as 9 to 12 years, high school or vocational education. More education is defined as less than 12 years, higher education.

Abbreviations: HR, hazard ratio; ref, reference.