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Title: CANCER EVENTS IN BELGIAN NURSING HOME RESIDENTS (NHR): An EORTC prospective cohort study.

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Abstract: Background: This prospective multicenter cohort study aimed to describe cancer events, referral patterns and motives for non-referral to advanced oncological care, anticancer treatments and outcome in nursing home residents (NHR).

Methods: The study was performed in 39 nursing homes from the Armonea network in Belgium, covering 4262 nursing home beds. All NHR in these homes were prospectively followed during 1 year for occurrence of cancer events (diagnosis or clinical suspicion of a new cancer or progression of a known cancer). After training, each site's local staff identified NHR with cancer events in collaboration with the treating general practitioner (GP). NHR with cancer events were included after informed consent, and data about general health and cancer status were collected every 3 months up to 2 years.

Findings: In only 9 NHR, a cancer event was recorded during follow-up including 5 new (suspected or diagnosed) cancer events (incidence rate = 123/100.000 NHR per year) and 4 NHR with (suspected or diagnosed) progressive disease. Of these 9 NHR (median age 87 years, range 72-92), 3 died around 1 month after inclusion in the study and median survival was 4 months. Identified cancer types were head and neck, breast, urogenital, gastrointestinal, skin and of unknown primary origin. In 4 NHR with suspected cancer, no diagnostic procedure was performed, and in 5 no anticancer treatment was started.

Conclusion: Clinically relevant cancer events (potentially requiring diagnostic or therapeutic action) occur at a much lower frequency in NHR than expected from cancer incidence data in the general older population. Although some underreporting of cancer events cannot be excluded, this prospective study supports several previous retrospective observations that cancer events are rare in very frail older persons. Moreover,

diagnostic and therapeutic actions for (suspected) cancer events are often not undertaken in this population.

Funding: sponsored by Armonea.

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CANCER EVENTS IN BELGIAN NURSING HOME RESIDENTS (NHR): An EORTC prospective cohort study.

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Authors: summary

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Abstract

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Introduction

Cancer is a disease of the elderly. Cancer incidence is 11-fold higher in persons over the age of 65, than in younger individuals¹. Approximately 60% of all new cancers and 70% of cancer mortality occurs in people older than 65 years². Moreover, due to the aging of the population in the Western world the number of elderly people is progressively increasing and therefore the number of older cancer patients is expected to rise¹. Despite this rapid increase in cancer incidence and cancer-related mortality with age, our knowledge about aging and cancer and about optimal treatment for older cancer patients is still far from adequate. A key problem in geriatric oncology research is the important selection bias because very old/frail patients are very rarely included in clinical trials^{3,4}.

Changes in the patterns of health care delivery have shifted the care of the elderly from acute care settings to the community and long-term care facilities. As the European population ages, more people will become nursing home residents (NHR), many of whom are expected to develop cancer based on their chronological age⁵. Although cancer might be very common in older NHR, it is poorly studied. Little information is available regarding diagnostic and therapeutic approaches and cancer outcomes, and also about the impact of cancer diagnosis on their health-related quality of life (HRQoL)^{5,6}. It is expected that many older patients with (suspected) cancer in nursing homes are not referred to hospitals or cancer centers for further diagnostic tests and/or treatments. In fact, a recent Dutch study has shown that 33% of elderly care physicians reported not having referred the last nursing home patient suspected with breast cancer to a hospital for diagnosis⁷. The motivations for this could be manifold and associated with patient's fitness, life expectancy and the expected benefit from further diagnostic and therapeutic procedures.

For these reasons, we designed a prospective study in NHR in Belgium including patients with and without known active cancer where a diagnostic/treatment decision had to be taken, focusing on incidence of cancer events, demographics, referral patterns and motives for non-referral, diagnostic procedures, anti-cancer treatments and outcome.

Methods

A prospective observational cohort study was designed and performed by the elderly task force (ETF) of the European Organisation for Research and Treatment of Cancer (EORTC). The study was approved by the ethics committee from the University Hospitals Leuven and registered at clinicaltrials.gov (NCT01910376). The study took place in nursing homes of a Belgian nursing home organisation called Armonea (www.armonea.be) and was approved and supported by the board of Armonea. Thirty-nine nursing homes were selected for the cancer cohort (see appendix 1) covering 4262 nursing home beds. The physicians and nurses in Armonea use a uniform medical file system and follow-up procedure for all the nursing homes allowing uniform patient documentation and data collection in the different nursing homes.

The main inclusion criterion was being resident in one of the 39 nursing home during the study period. New cancer events were defined as one of the following: 1/ a strong clinical suspicion (based on physician's judgement) of a new cancer where a diagnostic or therapeutic intervention could be taken; 2/ a strong clinical suspicion (based on physician's judgement) of progression of a previously known cancer where a diagnostic or therapeutic decision had to be taken; 3/ proven diagnosis of a new cancer where a diagnostic or therapeutic decision could be taken; 4/ proven diagnosis of progression of a previously known cancer where a diagnostic or therapeutic decision could be taken. Since we expected that not all cancer events would be clinically or pathologically proven, and would not always be followed by a diagnostic or therapeutic procedure, we decided to register both proven cancer events as well as clinically suspected events, based on the treating/responsible physician's judgement. All invasive cancer types and all histologies were eligible. Patients who were suspected and diagnosed with cancer during routine medical examinations (in nursing home or externally), or during (external) hospitalization (but with residence in one of the nursing homes and return to the nursing home after hospitalization) were eligible.

The ETF prepared information leaflets for patients and families, informed consent documents, a powerpoint slide deck for collaborators, a paper Case Record Form (CRF) for each case, and an information letter for the treating physicians of each nursing home (see appendix 2). If the resident and/or relatives agreed, a formal informed consent was signed by the resident (or the legal representative if not possible/feasible for the resident). Nursing homes were also asked to record the number of suspected cancer events where informed consent was refused.

The study was launched in 2 pilot nursing homes on 28/10/2014 and 14/11/2014. The principle investigator and EORTC delegates personally visited these 2 nursing homes for explanation to the local team. As no unexpected

practical problems occurred, the study was opened in the remaining 37 nursing homes on 17/3/2015. Five meetings were organised with all directors and/or head nurses of the 37 nursing homes prior to the start. An extensive information package as described above was provided to all nursing homes. For each nursing home, the director and head nurse were the primarily involved persons who informed their staff and treating physicians in their nursing homes.

After inclusion, prospective data collection was done through a questionnaire that was completed by the dedicated nurse and the treating general practitioner (GP) in the nursing home. Medical documents from hospitalization/specialist consultation were also used if available. At baseline, the following general parameters were recorded: patient characteristics (sex, age, weight, height, performance status (PS), date of admission to nursing home, list of comedication), geriatric evaluation (ADL scale, plus 2 cognitive items linked to the Belgian Activities of Daily Living (ADL) scale, Minimental state examination (MMSE)), Health related quality of life (HRQoL: questions 29 and 30 from EORTC QLQ-C30) if the patient was able to complete this, results of advance care planning, Porock 6-month mortality predictor scale (a scale specifically developed for a nursing home population; <http://eprognosis.ucsf.edu/porock.php>), Charlson comorbidity index (for details, see appendix 3). Most of these parameters were already part of routine evaluation in the Armonea nursing homes. Concerning cancer-specific data, the following parameters were collected: type of cancer, stage, date of (suspected) diagnosis, diagnosed before or after admission to the nursing home, diagnostic approach planned, therapeutic strategy planned, referral patterns to specialist, motives for non-referral. Armonea appointed a dedicated co-worker who took care of all the communication between the individual nursing homes, and the EORTC datacentre and research team. All patient data were anonymised by Armonea before being sent to EORTC.

Participant accrual stopped exactly 1 year after initiation in each nursing home. After enrollment in the study with a cancer event, participants were prospectively followed every 3 months for evolution in activities of daily living (ADL), cognition and health related quality of life (HRQoL), new cancer events and treatments, diagnostic and treatment procedures, and survival. Participants with a cancer event were followed until death or exit from the nursing home or for a maximum of 2 years.

The incidence rate of cancer (primary endpoint) was calculated as all (new) cancer events per 100,000 person years. Other endpoints, i.e. demographics, referral patterns and motives for non-referral, anti-cancer treatments and outcome (evolution in ADL, cognition, HRQoL and survival) in NHR were analysed by descriptive statistics. Median overall survival (OS) was estimated by using the Kaplan-Meier technique after all patients had been followed for 2 years.

Role of the funding source: Armonea, a Belgian nursing home network, provided financial support to EORTC.

Results

The study was launched in 2 pilot nursing homes on 28/10/2014 and 14/11/2014 that stopped accrual exactly 1 year after starting. The remaining 37 nursing homes started accrual on 17/3/2015 until 16/3/2016. The 39 nursing homes covered 4262 nursing home beds during that period. During the whole period, 9 cancer cases were registered which converts to an incidence rate of 222 per 100,000 NHR per year. The 9 cases included 5 new cancer events (corresponding to an incidence rate of 123 new cancers per 100,000 person-years) and 4 NHR with (suspected) progressive disease. The nursing homes reported no cases with (suspected) cancer events where informed consent was refused by the patient and/or family.

Table 1 summarizes the details on the 9 cancer cases. There were major differences in diagnostic and therapeutic approach, and also in survival. Two patients had 2 tumors. Tumour types included cancer of the head and neck (N=3), breast (N=2), urogenital (N=2), gastrointestinal (N=1), skin (N=1) and of unknown primary origin (N=1). In 4 of 9 NHR with suspected cancer, no diagnostic procedure was performed, and in 5 no anticancer treatment was started. Median survival was 4 months. Two of four patients who received anticancer treatment died within one month (both received treatment with curative intent). Of five patients who did not receive anticancer treatment, three died within 4 months, one after 17 months and one after 23 months.

Discussion

This study aimed for the first time to prospectively evaluate cancer events in a large nursing home population. Surprisingly, only 9 cancer events were recorded during 1 year period in a population of > 4000 NHR including 5 new (suspected or diagnosed) cancer events, accounting for a new cancer incidence of 123 per 100,000 person-years. This number of new cancer events in NHR was much lower than could be expected from epidemiological data. Data from the population-based Netherlands Cancer Registry indicate a cancer incidence rate of 2566 per 100,000 person-years in 2015 among those aged 75 or older (www.cijfersoverkanker.nl); specified per age group, this is 2514/100.000 for age 75-79, 2725/100.000 for age 80-84, 2613/100.000 for age 85-89, 2166/100.000 for age 90-94, 2013/100.000 for 95+. It should be acknowledged that this population contains both NHR and non NHR, but it is estimated that the NHR represent only about 10% in this population. In Belgium with a total population of about 10 Million inhabitants, 125.000 elderly lived in nursing homes in 2010 with a median age of 86 years (<https://www.kce.fgov.be/nl/toekomstige-behoefte-aan-residenti%C3%ABle-ouderenzorg-in-belgi%C3%AB-projecties-2011-2025>). In summary, the cancer incidence numbers in the general older population (independent of living place) are about 20 times higher than the incidence rate that was found in NHR in our study. At first sight, the numbers may appear inappropriately low. However, more and more (retrospective) data suggest that cancer incidence increases with age, but seems to decline again in the very old⁹. The concept of “Peak and decline of cancer incidence in the oldest old” has been formerly identified⁹ and several epidemiologic series have demonstrated a shrinkage of global cancer incidence behind a plateau laying in the 80-90 years range in women and in the 75-85 years range in men. The same was found in the Netherlands Cancer Registry, where the incidence of cancer in 2015 first increased to 2725/100,000 in age group 80-84 years, whereafter the incidence rate decreased to 2013/100,000 in those aged 95 or older (www.cijfersoverkanker.nl). However, even when compared to population-based data among the oldest age groups, the incidence rate of new cancer events in our NHR cohort was about 20 times lower. Another important observation is that 2 autopsy studies in very old men/women who died without a known cancer, showed a very low rate of invasive cancer. In the study from Stanta¹⁰, a group of 507 autopsied elderly was analyzed, divided in three age groups: 75-90 years, 95-99, and over 99 (centenarians). The prevalence of cancer was 35% among the younger persons and 20% and 16% respectively for those aged 95-99 and for the centenarians. The prevalence of metastases was 63% for tumors occurring in persons aged 75-90, 32% in persons aged 95-98, and 29% in the centenarians. In a second autopsy study¹¹, findings of 140 centenarians of the age range of 100-109 years were compared to those of 96 elderly subjects of the age range of 75-95 years. A lower prevalence (16.3% vs. 39.0%), as well as a slower and less aggressive evolution of neoplastic pathologies (frequency of metastases: 26.0% vs. 55.0%) were found in the centenarians, as compared to the general aging population. These data again confirm our observation that cancer events in very old/frail people are much less frequent than previously thought.

There may be several possible explanations for the low incidence rate of (suspected) cancer events among NHR. The most obvious one is *underreporting* of cancer events in the oldest old because of much less screening/diagnostic efforts in very old/frail populations. Indeed, many authors have hypothesized that the oldest and most vulnerable patients are excluded from cancer diagnosis, either because of general health problems (delirium, depression, apathy, falls...), competing risks of death (comorbidities) or because of active restrictions against such diagnosis from patients or their family and from their general practitioners. Therefore, in this project, cancer event reporting was promoted through a communication campaign towards NH nurses, physicians, and general practitioners. Moreover, also suspicion of cancer, without formal diagnosis, was prospectively assessed.

Consequently, one may consider the risk of major underdiagnosis as limited.

An *environmental* hypothesis, namely the decreased incidence of cancers related to environmental toxics (in particular professional exposure), to addictions (tobacco, alcohol) as well as to sexual activity (cervix cancers due to HPV viruses) may play some role as well but is unlikely to explain all the effect.

A genetic hypothesis, namely the selection of oldest beings having “*protective*” *genetic mutations* against the increasing mutational and/or epimutational load has also been considered. According to the the mutation burden theory, aging and cancer have their origin in the same pathways and such protective (epi)genetic changes should both protect from aging-related diseases and cancer (Medawar, 1952). However, one may consider that NHR usually display pathological aging, and should not be considered as genetically selected fit elderly.

Our results are in good accordance with the *hyperfunction theory of aging* which proposes that aging phenotypes are the consequences of two periods of time following each other¹². Firstly, the hyperfunction period, leading to the overstimulation of physiological processes, eventually leading to atherosclerosis by overstimulation of arterial smooth muscle cells, osteosclerosis by osteoclasts activation, in part driven by the activation of the TOR (Target of Rapamycin) pathway. Secondly, the malfunction period, associated with a shrinking of those physiological processes, characterized by a pathological aging (“decline”) but associated with a decreased incidence of cancer.

When looking at the cellular level, *cellular senescence* is considered a fundamental protection mechanism against cellular damage and oncogenesis¹³. There is a well known dilemma for individual cells if chromosomal damage occurs: cells may be prudent and choose the senescence pathway, implying growth arrest and diminished metabolic activity. Or, alternatively, the cell may choose to accept the chromosomal damage and continue proliferation, but the risk exists that this damage is oncogenic and results in a malignant cell clone and eventually cancer development. Thus, the senescence program shuts down damaged and potentially harmful cells. This cancer protection mechanism is, however, a double-edged sword: due to their lack of regenerative capacity, the accumulation of senescent cells leads to failure of organ homeostasis/function and is in fact the driving force in tissue aging. It could be stated that aging is the price a human body needs to pay for not getting cancer. This leads to the hypothesis that frail older people, who are more prone to ‘senescence’, might be less likely to develop cancer, while more fit elderly might be more predisposed to develop cancer.

When looking in detail into the diagnostic and therapeutic approach to these 9 cases, we observed significant heterogeneity in terms of diagnostic procedures, therapeutic management and survival. In 4 of them, no diagnostic procedure was performed, and in 5 no anticancer treatment was started. It is questionable whether the 5 residents who didn’t receive anticancer therapy, would have benefitted if some kind of anticancer therapy would have been started. Breast cancer and prostate cancer for instance, are generally quite easily controlled for significant time periods with ‘easy’ drugs such as antihormone therapy, and ‘undertreatment’ should be avoided. On the other hand, 2 of 4 patients who received anticancer treatment died within one month (both received treatment with curative intent) so it is also crucial to avoid overtreatment in this population. Median survival was generally short, but variable, and for NHR with longer life expectancy, appropriate cancer diagnosis and treatment may provide some benefit. The low number of cancer events precludes detailed analysis and interpretation of the results. Anyhow, the diagnostic approach seems much less extensive than in younger persons, which is not surprising.

This study has several strengths: it is the first prospective evaluation of cancer events in a frail nursing home population. The collaboration of a large nursing home network with uniform working procedures and management allowed the inclusion of a very large cohort. There are also limitations: our study did not evaluate formal incidence or prevalence of cancer. We decided to focus rather on clinically relevant possible ‘cancer-related events’ (that required a diagnostic and/or therapeutic procedure) since we believe that these events are much more relevant for individual nursing home residents, than pure incidence or prevalence data from new cancer cases that may or may not be clinically relevant (for instance, indolent prostate cancer is an irrelevant finding in a frail NHR). An important potential limitation and bias is underreporting of cancer events. We were well aware of this risk, and undertook all possible actions to prevent underreporting as much as possible. The study was organized top-down: the Armonia head quarters strongly supported this project (conceptually and financially), and all nursing home directors and head nurses were personally involved. While (formal) diagnosis of a cancer event is objective, we acknowledge that ‘physician’s judgement’ of strong clinical suspicion of a cancer event is more subjective. Given the fact that treating physicians and relatives mostly minimize diagnostic procedures in very frail persons, we considered this the only possibility to collect valuable information on this patient population. We certainly cannot exclude a certain extent of underreporting in this study, but the strong involvement of all nursing homes makes significant underreporting of clinically relevant cancer events unlikely.

In conclusion, this study for the first time prospectively evaluated cancer events in a large nursing home population. Clinically relevant cancer events (new diagnosis or progression of a previously known cancer) occurred at extremely low frequency. Although some underreporting of cancer events cannot be excluded, our findings

support several previous observations that cancer events are much less frequent and problematic in very frail older persons than previously expected. This information is important for health care organization within nursing homes. Moreover, diagnostic and therapeutic actions for (suspected) cancer events are often not undertaken in this population.

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Contributors' statement

All authors contributed to the design of the study and interpreted the data. HW wrote the manuscript which was reviewed and approved by all coauthors.

Declaration of interest

The authors don't have a conflict of interest related to this study.

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Table 1: Patient and cancer characteristics of the 9 (suspected) new cancer events in Nursing home residents (NHR)

Patient	1	2	3	4	5	6	7	8	9
Age (years)	92	86	85	81	80	89	89	72	86
sex	Female	Female	Male	Male	Female	Female	Male	Female	Female
Weight (kg)	59	86		97	62	83	43	59	46
MMSE (0 worst score, 30 best score)	18	30	25	21	29	23	29	25	19
Katz ADL score (.. worst score, .. best score)	20	16	18	19	8	15	17	10	20
Cognition (2 best score, 8 worst score)	6	4	2	4	2	3	2	2	2
Porock scale									
Written ACP by patient available	Yes	Yes	Yes	Missing	Missing	No	Yes	Yes	Missing
Written ACP by physician available	Yes	Yes	Yes	No	No	No	Yes	Yes	No
ACP: relative involved?	No	Yes	Yes	Missing	Missing	Yes	Yes	Yes	Missing
Number of medications	4	7	4	15	Missing	14	7	10	9
QoL: general health status (1 worst score, 7 best score)	4	3	3	4	4	4	3	4	Missing
QoL: general quality of life (1 worst score, 7 best score)	4	4	3	4	4	4	2	5	Missing
Charlson Comorbidity Index (0 = no severe comorbidities)	2	0	0	2	8	1	1	2	1
Cancer setting	Diagnosis of new cancer	Suspicion of progressive disease	Suspicion of new cancer	Diagnosis of progressive disease	Diagnosis of new cancer	Diagnosis of progressive disease	Diagnosis of new cancer	Diagnosis of progressive disease	Suspicion of new cancer
Tumor type	Gastro-intestinal	Breast	Prostate	Head and neck: now relapse in local and distant lymph nodes	Angiosarcoma in breast	Head and neck; now relapse in skin	Head and neck; and gingiva; metastases suspected in lung and colon	Bladder	Unknown primary (thoracic mass)
How was the tumor diagnosed?	Hospitalization	GP	GP	GP+referral	GP+referral	GP+referral	GP+referral	Hospitalization	Hospitalization
Clinical findings		Palpable mass/lymph nodes; visible tumor	General worsening; anorexia; urinary retention	Visible tumor		Visible tumor	Palpable mass/lymph nodes; visible tumor; pain		Anorexia
Laboratory findings	Blood count; elevated tumor markers		Elevated tumor markers					No details	
Medical imaging findings	CT-scan			CT-scan	Mammography			No details	CT-scan

Histological diagnosis				Biopsy	Biopsy	Biopsy	Biopsy	No details	
GP planning of diagnostic procedure and reason why not	No (old patient, bad health, no benefit)	Yes	No	Yes	Yes	Yes	Yes	no (comes from the specialist)	No (bad health, no benefit, family refusal)
Referral to a specialist and reason why not	No (old patient, bad health, no benefit)	Yes	No (bad health, no benefit, very depressed patient)	Yes	Yes	Yes	Yes	Yes	No (family refusal)
Any anticancer treatment started, reason why not, kind of treatment, purpose	No (old patient, bad health, no benefit)	No (patient refusal)	No	Yes (radiotherapy with curative intent)	Yes (surgery With curative intent)	Yes (radiotherapy and surgery with curative intent)	No (old patient, bad health, no benefit)	Yes (surgery with palliative intent)	No (no benefit, lack of symptoms, family refusal)
Any symptom control therapy started	Yes (pain killers)	No	No	Yes (pain killers)	No	Yes (pain killers and corticosteroids)	Yes (pain killers and antiemetics)	Yes (pain killers)	No
Case discussed at a MTD	No	Yes	No	Yes	Yes	Yes	Yes	Unknown	Unknown
GP present at the MTD		No		No	No	No	No		
Survival status	Dead	Dead	Dead	Dead	Alive	Dead	Dead	Alive	Dead
Survival (months) from signature of informed consent to death or last follow-up date	3	17	4	1	24	1	1	28	23

MMSE = minimal status examination; ACP = advance care planning ; GP = general practitioner ; MTD = multidisciplinary team discussion