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# Cancer and frailty in older adults: a nested case-control study of the Mexican Health and Aging Study

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**Abstract**
*Purpose* Understanding how the convergence between chronic and complex diseases—such as cancer—and emerging conditions of older adults—such as frailty—takes place would help in halting the path that leads to disability in this age group. The objective of this manuscript is to describe the association between a past medical history of cancer and frailty in Mexican older adults.
*Methods* This is a nested in cohort case-control study of the Mexican Health and Aging Study. Frailty was categorized by developing a 55-item frailty index that was also used to define cases in two ways: incident frailty (incident >0.25 frailty index score) and worsening frailty (negative residuals from a regression between 2001 and 2012 frailty index scores). Exposition was defined as self-report of cancer between 2001 and 2012. Older adults with a cancer history were further divided into recently diagnosed (<10 years) and remotely diagnosed (>10 years from the initial diagnosis). Odds ratios were estimated by fitting a logistic regression adjusted for confounding variables.
*Results* Out of a total of 8022 older adults with a mean age of 70.6 years, the prevalence of a past medical history of cancer was 3.6 % ($n=288$). Among these participants, 45.1 % had been diagnosed with cancer more than 10 years previously. A higher risk of incident frailty compared to controls [odds ratio (OR) 1.53 (95 % confidence interval (CI) 1.04–2.26, $p=0.03$); adjusted model OR 1.74 (95 % CI 1.15–2.61, $p=0.008$)] was found in the group with a recent cancer diagnosis. Also, an inverse association between a remote cancer diagnosis and worsening frailty was found [OR = 0.56 (95 % CI 0.39–0.8), $p=0.002$; adjusted model OR 0.61 (95 % CI 0.38–0.99, $p=0.046$)].
*Conclusions* Cancer is associated with a higher frailty index, with a potential relevant role of the time that has elapsed since the cancer diagnosis.
*Implications for cancer survivors* Cancer survivors may be more likely to develop frailty or worsening of the health status at an older age. This relationship seems especially evident among individuals with a recent oncological diagnosis. Health professionals in charge of older adult care should be aware of this association in order to improve outcomes of older adults who survived cancer.

**Keywords** Oncogeriatrics · Frailty · Chronic disease · Disability

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## Introduction

It is estimated that more than 40 % of individuals will be diagnosed with cancer during their lifetimes [1]. Fortunately, the advances in surgical techniques and medical treatments have significantly diminished cancer mortality over the past few decades despite of the increasing incidence of oncological diseases. As a result, several million individuals live with a medical history of cancer. Furthermore, due to the increase in cancer survival rates and the aging of the population, the number of cancer survivors will continue to increase [2, 3].

Frailty is a condition that compromises a person's capacity to respond adequately to both physical and psychological stressors, exposing the individual to a worsening of his/her health status [4]. Frailty has proven to be a hallmark of aging but its clinical significance remains an enigma [5]. Moreover, it is debated just how the interaction between morbidity and frailty takes place [6]. This interaction is of particular interest in the case of those with a history of cancer. Currently, the clinical application of the concept of frailty in oncology consists of the identification of frail and fit individuals as part of the decision-making process for their treatment, with preliminary results of such efforts particularly promising [7–9]. However, little is known about how the past medical history of cancer (for example, cancer that occurred in early adulthood) and frailty among survivors at advanced age are related. The limited evidence on the topic suggests that older cancer survivors may present an increased likelihood of being frail or disabled when compared with older adults without cancer background [10].

The aim of this study is to describe the association between the medical histories of cancer and frailty in a representative sample of older adults enrolled in the Mexican Health and Aging Study (MHAS) cohort. In the present study, frailty is operationally defined according to the model proposed by Rockwood and colleagues [11], which was specifically designed to capture the age-related accumulation of deficits from a broader biopsychosocial perspective of health [12].

## Methods

### Setting and participants

This study is a secondary analysis of the first (2001) and third (2012) waves of the MHAS, a cohort study conducted in Mexico, whose aim and design are available elsewhere [13, 14]. Briefly, there are three waves of this study with a probabilistic sample of Mexican adults 60 or more years of age (2001, 2003, and 2012). A set of questionnaires (socio-demographic characteristics, health-related issues, access to health services, cognitive performance, functional status, and financial resources) were governed to all the participants. In addition, each wave included a sub-sample with anthropometry and blood samples.

A total of 8022 subjects who completed the third wave assessment was considered for the present analyses ($N = 15,182$), after exclusion of those who died during the follow-up ($n = 2742$), were lost to follow-up or unable to complete the required evaluations ($n = 3572$), or were younger than 60 years of age in 2012 ($n = 846$).

### Frailty index construction

A number of categories were included to construct a 55-item frailty index (FI). Mobility, activities of daily living (ADL) and instrumental ADL (IADL) were included in the first set of deficits. The second category of measures included in the measure of frailty included comorbidities (hypertension, diabetes mellitus, chronic obstructive pulmonary disease, stroke, arthritis, falls, fractures, vision problems). Another category included symptoms perceived by participants during the 2 years prior to the assessment (fatigue, respiratory symptoms, involuntary urine loss, gastrointestinal symptoms, pain). Depressive symptoms were also included as a set of seven dichotomous items generated by specific questions related to mood. Finally, perceptions such as locus of control, self-rated current health status, and 2-year comparison self-rated health were considered as the last set of deficits for developing the broad measure of FI. The frailty index was composed following a standardized procedure described by Searle et al. [15], which includes transforming each variable into a score ranging from 0 (deficit absent) to 1 (deficit present) with possible intermediate scores. All scores indicating a deficit were added and then divided by 55 (total number of deficits in the current list) for each subject (Supplementary Table 1).

Two approaches to the analysis were taken for studying the incidence of frailty (defined as a frailty index $\geq 0.25$ as previously described [16]) and the worsening of the frailty status). Specifically, for frailty incidence, only participants with a $FI < 0.25$ in 2001 ($n = 5751$) were included. A participant was defined as having developed frailty during the follow-up if presenting a $FI \geq 0.25$ at the 2012 wave. For the measure of increased severity of frailty (i.e., worsening), The FI score was defined as subjects with a negative residual in a fitted regression model predicting the latest wave (2012) of FI from the baseline (2001) FI.

### Cancer assessment

Cancer was assessed by a single question, identically administered at the two waves. In both 2001 and 2012 assessment visits, the subject was asked "Has a doctor or any other health personnel diagnosed you with cancer?" Answering "yes" to this question defined the exposition of the subject. In 2012, a

second question regarding the year of diagnosis of a previous cancer was also asked.

Participants with a history of cancer were divided into two groups according to the time of the diagnosis: diagnosis of cancer made more than 10 years before (CH10+) versus 10 or less years before (CH10−). Cancer type was classified according to anatomic site including gastrointestinal, gynaecologic, prostate, breast, and other sites. Finally, data on treatment for cancer received (i.e., chemotherapy, surgery, and/or radiotherapy) was also registered.

### Other variables

In addition to variables included in the 55-item FI, other variables were measured in order to adjust for confounding. Socio-demographic, health behavior, and psychosocial stress variables included age, sex, marital status, years in school, smoking status, and negative events. Negative events were present if the subject reported at least one event from a list of ten negative events (moving to another address; changing city; having lived in the United States of America; having a medical history of stroke, heart attack, major surgery, or hospital admission; having been a victim of a natural disaster or a victim of a crime or accident in the previous 11 years). As shown in previous studies, negative events are associated with worsening of health status of older adults, and this data set does include a number of negative events that we were able to provide control for this confounder [17]. Similarly, given the prevalence in older adults, cognitive function was assessed with a brief version of the cross-cultural cognitive examination [18]. This test is composed of five subtests, and cognitive impairment was defined by the failure in two or more of these.

### Statistical analysis

Bivariate analyses were carried out in order to assess the difference between groups of frailty status using Chi squared test for nominal variables and *t* test where appropriate. Multiple logistic regression models to test the association between cancer and frailty were performed, unadjusted and adjusted for age, sex, marital status, years in school, smoking status, at least one negative event in the previous 11 years, cognitive decline, and cancer-related therapy (chemotherapy, surgery, and/or radiotherapy). In order to test the consistency of the FI, the models were run with cancer included in a 56-item FI in order to assess changes in estimates. All analyses were performed with the statistical software package STATA 13.1© (Texas, USA).

### Ethical considerations

The Institutional Review Boards or Ethics Committees of the University of Texas Medical Branch in the United States, the Instituto Nacional de Estadística y Geografía, the Instituto Nacional de Salud Pública, and the Instituto Nacional de Geriatría in Mexico approved the study. All study subjects signed an informed consent form.

## Results

Out of a total of 8022 subjects, the mean age was 70.6 years (standard deviation [SD] = 7.4), and 56.6 % ($n = 4547$) were women. Overall, 58.2 % of subjects ($n = 4669$) were married, and the mean number of years of formal education was 4.5 ($SD = 4.3$). A total of 5.7 % ($n = 469$) of the older adults had experienced at least one negative event in the previous 11 years. Regarding smoking status, 63 % ($n = 5061$) had never smoked, 27.1 % ($n = 2175$) were previous smokers, and 9.8 % ($n = 786$) were current smokers. Cognitive impairment was present in 35.9 % ($n = 2880$) of the whole sample.

There was a significant difference (mean difference = 0.042, $SD = 0.11$) between the baseline FI (mean = 0.196, $SD = 0.108$) and the follow-up (mean = 0.239, $SD = 0.114$) assessment (paired *t* test <0.001). The deficit associated with the higher impact on the FI mean score was self-rated health status. The lowest item was having a missing limb (in both waves; Supplementary Table 1). At follow-up, 29.9 % of the subjects ($n = 1721$) showed FI ≥ 0.25.

The prevalence of a past medical history of cancer (from 2001 up to 2012) was 3.6 % ($n = 288$). Among these participants, 45.1 % had cancer diagnosed greater than 10 years (CH10+). The most prevalent type of cancer was gynecological cancer 33.6 % ($n = 97$), followed by prostate cancer 15.9 % ($n = 46$) and breast cancer 14.9 % ($n = 43$). Among participants reporting a past medical history of cancer, 8.6 % ($n = 25$) had received chemotherapy, 15.6 % ($n = 45$) had surgery, and 8.6 % ($n = 25$) had undergone radiotherapy.

In the bivariate analysis (Table 1), neither cancer nor cancer type (according to time from diagnosis) was associated with FI.

The results of models predicting the weight of cancer on frailty were not statistically significant (Table 2). For the analyses aimed at exploring the incidence of frailty, the only significant association was reported for the participants diagnosed for less than 10 years (CH10−), which showed a higher risk of incident frailty compared to that in the controls [odds ratio (OR) 1.53 (95 % confidence interval (CI) 1.04–2.26, $p = 0.03$); adjusted model OR 1.74 (95 % CI 1.15–2.61, $p = 0.008$)]. Regarding cancer types and progression of frailty, when contrasting subjects with no previous history of cancer with those who had a cancer diagnosis for less than 10 years (CH10−), there was no significant association.

**Table 1** General characteristics of the sample by frailty status (incident or worsening index)

| | Incident frailty ($N=5751$) | | | Worsening index ($N=8022$) | | |
|---|---|---|---|---|---|---|
| | FI < 0.25 ($n=4031$ [70.1 %]) | FI ≥ 0.25 ($n=1722$ [29.9 %]) | $p$ value | Not worse ($n=3702$ [46 %]) | Worse ($n=4320$ [53.8 %]) | $p$ value |
| Age, mean (SD) | 69.5 (6.7) | 71.6 (7.7) | <0.001 | 70.3 (7.3) | 71 (7.4) | <0.001 |
| Women, *n* (%) | 1864 (64.7) | 1014 (35.2) | <0.001 | 2443 (53.7) | 2104 (46.2) | <0.001 |
| Married, *n* (%) | 2604 (72.6) | 980 (27.3) | <0.001 | 1941 (41.5) | 2729 (58.4) | <0.001 |
| Years in school, mean (SD) | 5.6 (4.8) | 3.7 (3.7) | <0.001 | 3.8 (3.7) | 5.1 (4.7) | <0.001 |
| Smoking status, *n* (%) | | | | | | <0.001 |
| Never smoked | 2373 (68.7) | 1079 (31.2) | <0.001 | 2476 (48.9) | 2586 (51) | |
| Smoked | 1179 (70.3) | 496 (29.6) | | 894 (41.1) | 1281 (58.9) | |
| Currently smoke | 478 (11.8) | 146 (23.4) | | 332 (42.2) | 454 (57.7) | |
| At least one negative event, *n* (%) | 184 (54.4) | 154 (45.5) | <0.001 | 193 (41.9) | 267 (58) | 0.063 |
| Cognitive impairment, *n* (%) | 1283 (66.8) | 635 (33.1) | <0.001 | 1514 (52.5) | 1291 (47.4) | <0.001 |
| Cancer, *n* (%) | 120 (64.5) | 66 (35.5) | 0.092 | 146 (50.6) | 142 (49.3) | 0.115 |
| Type of cancer, *n* (%) | | | | | | 0.015 |
| Gastrointestinal | 12 (63.1) | 7 (36.8) | 0.557 | 13 (46.4) | 15 (53.5) | |
| Gynaecologic | 42 (68.8) | 19 (31.1) | | 61 (62.9) | 36 (37.1) | |
| Prostate | 21 (60) | 14 (40) | | 15 (32.6) | 31 (67.3) | |
| Breast | 18 (75) | 6 (25) | | 20 (46.5) | 23 (53.4) | |
| Other | 27 (57.4) | 20 (42.5) | | 37 (50) | 37 (50) | |
| Surgery, *n* (%) | 17 (68) | 8 (32) | 0.821 | 29 (64.4) | 16 (35.5) | 0.014 |
| Chemotherapy, *n* (%) | 6 (46.1) | 7 (53.8) | 0.151 | 14 (56) | 11 (44) | 0.322 |
| Radiotherapy, *n* (%) | 8 (57.1) | 6 (42.8) | 0.549 | 13 (52) | 12 (48) | 0.557 |
| Cancer categories (by time since last cancer diagnosis), *n* (%) | | | | | | 0.005 |
| Without cancer | 3910 (70.2) | 1655 (29.7) | 0.09 | 3556 (52.6) | 4179 (54) | |
| Cancer more than 10 years ago | 54 (70.1) | 23 (29.8) | | 78 (60) | 52 (40) | |
| Cancer in the last 10 years | 66 (60.5) | 43 (39.4) | | 68 (43) | 90 (56.9) | |

*FI* frailty index, *n* number, *SD* standard deviation

However, between the subjects without cancer and those who had a cancer diagnosis for more then 10 years (CH10+), a significant association was found [OR = 0.56 (95 % CI 0.39–0.8), $p=0.002$; adjusted model OR 0.61 (95 % CI 0.38–0.99, $p=0.046$)]. When comparing older adults with CH10+ versus CH10−, the OR was of 0.5 (95 % CI 0.31–0.8, $p=0.004$), losing significance in the adjusted model [OR 0.59 (95 % CI 0.69–1.34, $p=0.074$)] (Table 3). Estimates in models with the 56-item FI, which included cancer, provided similar results (data not shown).

## Discussion

The results of this population-based study revealed that cancer survivors may be more likely to develop frailty or worsening of the health status at an older age. In particular, the relationship between a history of cancer and frailty seems especially evident among individuals with a cancer diagnosis less than 10 years. This association was independent of other confounding variables.

The recent interest in the identification, prevention, and treatment of chronic sequels of cancer as well as the

**Table 2** Multiple logistic regression models (unadjusted and adjusted) for dichotomous 55-item frailty index and for worsening frailty index with cancer status

| | Unadjusted OR (95 % CI) | $p$ value | Adjusted OR (95 % CI)[a] | $p$ value |
|---|---|---|---|---|
| FI > 0.25 in follow-up | 1.29 (0.95–1.76) | 0.093 | 0.8 (0.37–1.76) | 0.593 |
| Worsening of the FI | 0.82 (0.65–1.04) | 0.116 | 0.87 (0.66–1.15) | 0.345 |

*OR* odds ratio, *CI* confidence intervals, *FI* frailty index

[a] Adjusted for age, sex, marital status, years in school, at least one negative event in the last 11 years, smoking status and cognitive decline, chemotherapy, surgery, and radiotherapy

**Table 3** Multiple logistic regression models (unadjusted and adjusted) for dichotomous 55-Item frailty index and for worsening frailty index with three categories of cancer status: without cancer, remote cancer, and recent cancer

| Analysis | Groups | Unadjusted OR (95 % CI) | *p* value | Adjusted OR (95 % CI)[a] | *p* value |
|---|---|---|---|---|---|
| FI > 0.25 in follow-up | Reference versus group 1 | 1 (0.61–1.64) | 0.98 | 0.81 (0.39–1.64) | 0.561 |
| | Reference versus group 2 | 1.53 (1.04–2.26) | 0.03 | 1.74 (1.15–2.61) | 0.008 |
| | Group 1 versus group 2 | 0.65 (0.35–1.21) | 0.18 | 0.46 (0.2–1.04) | 0.065 |
| Worsening of the FI | Reference versus group 1 | 0.56 (0.39–0.8) | 0.002 | 0.61 (0.38–0.99) | 0.046 |
| | Reference versus group 2 | 1.12 (0.81–1.54) | 0.463 | 1.03 (0.74–1.43) | 0.838 |
| | Group 1 versus group 2 | 0.5 (0.31–0.8) | 0.004 | 0.59 (0.95–2.96) | 0.074 |

Reference corresponds to the group without cancer

Group 1 corresponds to the group with cancer of more than 10 years since diagnosis

Group 2 corresponds to the group with cancer of 10 years or less since diagnosis

*OR* odds ratio, *CI* confidence intervals, *FI* frailty index

[a] Adjusted for age, sex, marital status, years in school, at least one negative event in the last 11 years, smoking status and cognitive decline, chemotherapy, surgery, and radiotherapy interaction

importance of maintaining or improving the longer-term function of cancer survivors has led to the identification several adverse outcomes as well as interventions directed at these problem areas. For example, recent work suggests that the use of primary healthcare services among post-treatment cancer survivors is greater than in age-matched controls—especially due to cancer-related fatigue [19]. However, other determinants of health status and disability, such as frailty, have been scarcely investigated, and reports focusing on elderly cancer survivor populations are even less.

In their 2009 report, Mohile and colleagues showed that a history of cancer was associated with ADL/IADL disability, frailty, and other adverse outcomes [10]. Such findings indicated the need to identify frailty in this group of patients, which is particularly exposed to a higher risk of multiple adverse health-related outcomes. However, this study was cross-sectional, and frailty measure was not as comprehensive when compared to the broader measure of FI used in the present study, in particular the ability of this index to provide measures of psychological health and its changes in older adults [12]. Even though there is an ongoing debate on how to best measure frailty in the clinical, the FI provides an instrument that can be derived from the clinical interview and includes a wide array of problem areas or deficits that reflect the complexity of the older adult who has survived cancer. The traditional metrics to determine the reliability and validity of this measure is required, and in the future, other instruments should also be tested, Nonetheless, the current measure of frailty was related to reported history of cancer diagnosis.

The association between cancer survivorship and frailty in older adults may be explained through several pathways, including the presence of iatrogenic damage (sequels of the adopted interventions) and residual chronic conditions due to cancer and aging. In other words, these individuals are dealing with the interacting effects of the biological and physiological changes of aging, multi-morbidity, and the effects of the cancer and its treatments. Biological aging is characterized by genetic instability, DNA repair imbalance, telomere shortening, epigenetic alterations, altered nutrient sensing, protein instability, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication, and inflammation.

These biological changes can lead to an overall decrease of the homeostatic reserve and subsequently to proneness to adverse outcomes. Such changes characterize frailty as well, and these challenges would certainly include the effects of cancer and its treatments, which seem to have lasting effects should the individual reach old age. Although some of the adverse effects may be caused by cancer itself, most appear to result from the effects of treatment, as in prostate cancer where the anti-androgen therapy leads to sarcopenia [20], but chemotherapy has the most pervasive effect [21]. Compared with the young individual in whom such changes may produce a "premature aging syndrome," in the older adult, these effects are superimposed with the age-related changes leading to frailty [22].

On the other hand, molecular pathways for understanding how interactions between frailty and cancer take place are still needed. Cancer is a disease that results from the accumulation of derangements in the genome of somatic cells. Cellular senescence is a process by which the cell attempts to limit oncogenic stress. This process is associated with degenerative as well as hyperplasic disorders like cancer. The healthy aging cell may be senescent as an evolutionary trait to avoid molecular alterations. Cells that senesce owing to oncogenic stress develop a senescence-associated secretory phenotype (SASP), which promotes a pro-inflammatory microenvironment [21]. In addition, frailty has been associated with systemic inflammation—and the SASP—which in turn could give a

biological explanation at the molecular level of the association between both processes [22, 23].

From the epidemiological point of view, as the number of elderly cancer survivors increase and as their oncological follow-up comes to an end, more of these patients will be referred for follow-up to primary or geriatric care units. Communication between the oncologist and the primary care physician is imperative to identify long-term consequences of cancer [24, 25]. Most primary care physicians would find it useful for the follow-up cancer care of these patients to have a patient-specific letter from the oncologist, expedited routes of referral, and expedited access to investigations for suspected recurrence and printed guidelines [26]. The national comprehensive cancer network provides guidelines for the long-term follow-up of these patients [27], but local guidelines are required. Nevertheless, the participation of the geriatrician would be necessary as a multidimensional approach to the survivor older adult patient, and to make particular emphasis in the detection and screening of frailty [8]. Cross-talk between disciplines certainly would reinforce the care of the older adult who has survived cancer.

Interestingly, the relationships between cancer and frailty with aging have been repeatedly suggested. If cancer can be seen in part as the result of the failure of aging cells, frailty has been indicated as a condition of biological aging. In this context, our findings are supportive of such a relationship by showing that cancer history is associated with an index of biological aging even years after the onset of cancer.

Regarding the protective association of a remote history of cancer (more than 10 years) for frailty, some explanations may be proposed. For instance, 30.8 % of the present population had been diagnosed with either prostate or breast cancer. Patients with these types of cancers may receive endocrine therapies for some years after the diagnosis as a first-line treatment. Endocrine therapies have been associated with the development of osteoporosis, as well as metabolic and body composition changes, including increased adiposity and sarcopenia [28], which may promote the occurrence of frailty. Also, patients with a recent cancer diagnosis have frequently been described as showing the presence of polypharmacy, a well-known phenomenon associated with frailty not only in healthy older patients but also in elderly cancer patients. Polypharmacy is understood as the consumption of more than three drugs, which in turn increases the probability of adverse drug reactions, adding new drugs, having inappropriate prescription, under-prescription and pharmacological interactions [29]. However, most patients with a history of cancer diagnosis more than 10 years ago in our country were not usually exposed to hormone therapy and may be less likely to have polypharmacy associated with cancer treatments. Furthermore, they are also less likely to show cancer recurrence. Finally, it is possible that participants with a remote history of cancer may have experienced less severe oncological conditions. On the other hand, those having more recently received the diagnosis may still be under treatment (potentially exposed to the adverse events of invasive/heavy interventions) and/or under the direct detrimental influence of the cancer.

It is important to highlight potential bias from self-reporting that could somehow invalidate these results. However, from an epidemiological point of view, self-reporting is a valid measure, and associations that hold in such large populations and after rigorous adjustment may diminish the impact of error in self-reporting [30]. In addition, our study lacks current cancer status, whether older adults are disease-free or with activity. There may also be differences among patients with different cancer types, with respect to the molecular biology, physiopathology, and treatment. This is of particular interest for hematological cancers, which are more frequent in adulthood and in particular during old age. Further studies should aim at differentiating consequences also of subtypes of cancer.

To our knowledge, this is the first study to assess the time elapsed since cancer diagnosis and is a more comprehensive view of frailty [10]. It raises a specific question about a potential survival effect that may lower the probability of being frail. While these relationships and associated biological plausibility require further confirmation, these results represent an important step toward understanding the role of cancer survivorship, aging, and frailty.

#### Compliance with ethical standards

**Conflict of interest** The authors declare that they have no competing interests.

**Ethical considerations** The Institutional Review Boards or Ethics Committees of the University of Texas Medical Branch in the United States, the Instituto Nacional de Estadística y Geografía, the Instituto Nacional de Salud Pública, and Instituto Nacional de Geriatría in Mexico approved the study. All study subjects signed an informed consent.

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