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Dipòsit Legal: L.1444-2015
http://hdl.handle.net/10803/314175

Universitat de Lleida

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Doctoral Thesis

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A thesis submitted in fulfilment of the requirements for the degree of Doctor in Estudis Avançats en Ciències Biomèdiques in

Ciències Mèdiques Bàsiques, Universitat de Lleida

January 2015, Lleida

Montserrat Martínez Alonso. *Cancer and quality of life. Breast Cancer overdiagnosis and design of an intervention to improve the quality of life of oncological patients in palliative care.* Doctoral Thesis. © January 2015

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Dedicated to the loving memory of my mother,
Julia Alonso Rodríguez.

1940 – 2013

ABSTRACT

BACKGROUND

Early detection of breast cancer (BC) with mammography may cause overdiagnosis and overtreatment, detecting tumors which would remain undiagnosed for a lifetime, and impacting on quality of life. The aims of this first area of study were: to model invasive BC incidence trends in Catalonia (Spain) taking into account reproductive and screening data; and to quantify the extent of BC overdiagnosis.

Quality of life is the most important outcome for advanced cancer patients in palliative care. The aims of this second area of study were: to perform a systematic review of all the clinical outcomes reported in peer-reviewed publications after the supplementation with D_3 or ergocalciferol (D_2); to assess serum vitamin D deficiency and its relationship with quality of life, fatigue, and physical and functional performance; and to design a randomized controlled trial to assess cholecalciferol (D_3) effectiveness in increasing quality of life.

METHODS

We modeled the incidence of invasive BC using a Poisson regression model. Explanatory variables were age at diagnosis and cohort characteristics (fertility rate, mammography use and year of birth). This model was also used to estimate the background incidence in the absence of screening. We used a probabilistic model to estimate the expected BC incidence if women in the population used mammography as reported in health surveys. The difference between the observed and expected cumulative incidences provided an estimate of overdiagnosis.

The systematic review included all the original research supplementing with D_2 or D_3 and reporting clinical outcomes. The search strategy was run in MEDLINE and SCOPUS. The cross-sectional study included 30 patients with the same inclusion/exclusion criteria as the VIDAFACT study. It was designed, implemented and analyzed using a bivariate analysis. We designed a randomised triple-blind phase II/III placebo-controlled multicentre trial (VIDAFACT, with trial registration number: EudraCT: 2013-003478-29) to establish the evidence for a beneficial effect of supplementing with 4,000 IU/day of D_3 to

advanced cancer patients in palliative care.

RESULTS

Incidence of invasive BC has increased among Catalan women, especially in birth cohorts from 1940 to 1955. These cohorts showed the highest increase in BC incidence rates (more than doubled) for ages 50 to 65 years. Screening use of mammography was significantly associated with BC incidence and overdiagnosis. Our estimates of overdiagnosis increased from 0.4% to 46.6%, for women born from 1935 to 1950.

The results of the systematic review contained no original research reporting the results of randomized controlled trials of effectiveness (phase III), and a very heterogeneous use of D_3 and D_2 in terms of dosage and treatment duration. The results of the cross-sectional study showed a significant association of fatigue and physical/functional performance with serum vitamin D levels, although there was no evidence of a direct association with quality of life. The first randomized controlled trial to assess the effectiveness of D_3 to improve the quality of life of advanced cancer patients in palliative care has been registered in the Spanish and European Medicines Agencies (AEMPS and EMA) and approved by the hospital ethical committee. The recruitment of patients will begin soon.

CONCLUSIONS

Estimates support the existence of overdiagnosis in Catalonia attributable to mammography usage. In view of the demonstrated risk of overdiagnosis, women should be clearly informed. Future research in BC screening should be oriented towards personalized screening and risk assessment tools.

The results from both the cross-sectional study in advanced cancer patients in palliative care and the systematic review on published outcomes from studies reporting on supplementation with vitamin D_2 or D_3, support the need for VIDAFACT to provide data about vitamin D supplementation effectiveness on improving overall quality of life.

RESUM

CONTEXT

La detecció precoç del càncer de mama (CM) mitjançant mamografia pot causar sobrediagnòstic i sobretractament, és a dir, la detecció de tumors que romandrien sense diagnosticar durant tota la vida, disminuint la qualitat de vida. Els objectius d'aquesta primera àrea d'estudi van ser: modelitzar les tendències d'incidència de CM invasius a Catalunya (Espanya), tenint en compte dades sobre fecunditat i cribratge; i quantificar el grau de sobrediagnòstic de CM.

La qualitat de vida és l'aspecte més important pels pacients amb càncer avançat en cures pal·liatives. Els objectius d'aquesta segona àrea d'estudi van ser els següents: dur a terme una revisió sistemàtica de tots els resultats clínics publicats que tractin sobre els malalts de càncer després de la suplementació amb D_3 o ergocalciferol (D_2); avaluar la deficiència de vitamina D en sèrum i la seva relació amb la qualitat de vida, la fatiga, i el rendiment físic i funcional; i dissenyar un assaig controlat aleatori per avaluar l'eficàcia de colecalciferol (D_3) en l'augment de la qualitat de vida.

MÈTODES

La incidència de CM invasiu es va modelar utilitzant regressió de Poisson. Les variables explicatives van ser l'edat al diagnòstic i les característiques de la cohort (taxa de fertilitat, ús de la mamografia i any de naixement). Aquest model també es va utilitzar per estimar la incidència en absència de cribratge. Es va utilitzar un model probabilístic per estimar la incidència de CM esperada si les dones en la població utilitzen la mamografia com s'informa en les enquestes de salut. La diferència entre les incidències acumulades observades i esperades proporciona una estimació del sobrediagnòstic.

La revisió sistemàtica va incloure tots els estudis originals en que els malalts van prendre D_2 o D_3 i van informar sobre els resultats clínics. L'estratègia de cerca es va realitzar en MEDLINE i SCOPUS. L'estudi transversal va incloure 30 pacients amb els mateixos criteris d'inclusió / exclusió que l'estudi VIDAFACT. Va ser dissenyat, implementat i analitzat utilitzant mètodes bivariants. Hem dissenyat un assaig triple cec aleatoritzat fase II / III controlat amb placebo i multicèntric (VIDAFACT, amb número de registre de l'assaig: EudraCT:

2013-003478-29) per establir l'evidència d'un efecte beneficiós de la suplementació amb 4.000 UI / dia de D_3 per als pacients amb càncer avançat en cures pal·liatives.

RESULTATS

La incidència de CM invasiu ha augmentat entre les dones catalanes, especialment a les cohorts nascudes de 1940 a 1955. Aquestes cohorts van mostrar el major augment en les taxes d'incidència de CM (més del doble) per a les edats de 50 a 65 anys. L'ús de la mamografia de cribratge es va associar significativament amb la incidència i sobrediagnòstic de CM. Les nostres estimacions de sobrediagnòstic van augmentar de 0,4 % al 46,6 %, per a les dones nascudes en 1935-1950.

Els resultats de la revisió sistemàtica no van detectar cap investigació original sobre els resultats dels assaigs controlats aleatoris d'eficàcia (fase III), però sí un ús molt heterogeni de D_3 i D_2 en termes de dosi i durada del tractament. Els resultats de l'estudi transversal van mostrar associació de la fatiga i el rendiment físic i funcional amb els nivells de vitamina D en sèrum, encara que no es van observar evidències d'una associació directa amb la qualitat de vida. El primer assaig controlat aleatori per avaluar l'eficàcia de D_3 per millorar la qualitat de vida dels pacients amb càncer avançat en cures pal·liatives ha estat registrat en les Agències de Medicaments espanyoles i europees (AEMPS i EMA) i aprovat pel comité ètic de l'hospital. En breu es començarà a reclutar pacients.

CONCLUSIONS

Les nostres estimacions recolzen l'existència de sobrediagnòstic a Catalunya atribuïble a l'ús de la mamografia. Atesa la presència demostrada de risc de sobrediagnòstic, les dones han de rebre informació clara sobre aquest. La investigació futura en el cribratge de CM s'ha d'orientar cap a eines d'avaluació de risc i detecció personalitzada.

Tant els resultats de l'estudi transversal en pacients amb càncer avançat en cures pal·liatives com els resultats de la revisió sistemàtica sobre els resultats publicats d'estudis que informen sobre la suplementació amb vitamina D_2 o D_3 en pacients amb càncer, donen suport a la necessitat de VIDAFACT per proporcionar dades sobre l'eficàcia en termes de qualitat de vida general.

RESUMEN

CONTEXTO

La detección precoz del cáncer de mama (CM) mediante mamografía puede causar sobrediagnóstico y sobretratamiento, es decir, la detección de tumores que permanecerían sin diagnosticar durante toda la vida, disminuyendo la calidad de vida. Los objetivos de esta primera área de estudio fueron: modelizar las tendencias de incidencia de CM invasivos en Cataluña (España), teniendo en cuenta datos de fecundidad y cribado de las cohortes estudiadas; y cuantificar el grado de sobrediagnóstico del CM.

La calidad de vida es el resultado más importante para los pacientes con cáncer avanzado en cuidados paliativos. Los objetivos de esta segunda área de estudio fueron los siguientes: llevar a cabo una revisión sistemática de todos los resultados clínicos publicados sobre enfermos de cáncer tras la suplementación con colecalciferol D_3 o ergoferol (D_2); evaluar la deficiencia de vitamina D en suero y su relación con la calidad de vida, la fatiga, y el rendimiento físico y funcional; y diseñar un ensayo controlado aleatorio para evaluar la eficacia de D_3 en el aumento de la calidad de vida.

MÉTODOS

Modelizamos la incidencia de CM invasivo utilizando un modelo de Poisson. Las variables explicativas fueron la edad al diagnóstico y las características de la cohorte (tasa de fecundidad, uso de la mamografía y año de nacimiento). Este modelo también se utilizó para estimar la incidencia basal en ausencia de cribado. Se utilizó un modelo probabilístico para estimar la incidencia de CM esperado si las mujeres en la población utilizaran la mamografía como se informa en las encuestas de salud. La diferencia entre las incidencias acumuladas observadas y esperadas proporciona una estimación del sobrediagnóstico.

La revisión sistemática incluyó todos los estudios originales que suplementaron con D_2 o D_3 e informaron sobre los resultados clínicos. La estrategia de búsqueda se realizó en MEDLINE y SCOPUS. El estudio transversal incluyó a 30 pacientes con los mismos criterios de inclusión / exclusión que el estudio VIDAFACT. Fue diseñado, implementado y analizado para aplicar un análisis bivariado. Hemos di-

señado un ensayo multicéntrico triple ciego aleatorizado fase II / III placebo-controlado (VIDAFACT, con número de registro: EudraCT: 2013-003478-29) para establecer la evidencia de un efecto beneficioso de la suplementación con 4.000 UI / día de D_3 para los pacientes con cáncer avanzado en cuidados paliativos.

RESULTADOS

La incidencia de CM invasivo ha aumentado entre las mujeres catalanas, especialmente en las cohortes nacidas de 1940 a 1955. Estas cohortes mostraron el mayor aumento en las tasas de incidencia de CM (más del doble) para las edades de 50 a 65 años. El uso de mamografía de cribado se asoció significativamente con la incidencia y sobrediagnóstico de CM. Nuestras estimaciones de sobrediagnóstico aumentaron de 0,4 % al 46,6 %, para las mujeres nacidas en 1935-1950.

Los resultados de la revisión sistemática no mostraron ningún resultado de ensayos aleatorios controlados de eficacia (fase III), y sí un uso muy heterogéneo de D_3 y D_2 en términos de dosis y duración del tratamiento. Los resultados del estudio transversal mostraron una asociación significativa de la fatiga y el rendimiento físico y funcional con los niveles de vitamina D en suero, aunque no se observó evidencia de una asociación directa con la calidad de vida. El primer ensayo controlado aleatorio para evaluar la eficacia de D_3 para mejorar la calidad de vida de los pacientes con cáncer avanzado en cuidados paliativos ha sido registrado en las Agencias de Medicamentos españolas y europeas (AEMPS y EMA) y aprobado por el comité ético del hospital. Se empezará a reclutar pacientes próximamente.

CONCLUSIONES

Nuestras estimaciones apoyan la existencia de sobrediagnóstico en Cataluña atribuible al uso de la mamografía. Dada la presencia demostrada de riesgo de sobrediagnóstico, las mujeres deben recibir información clara sobre éste. La investigación futura debe orientarse hacia herramientas de evaluación de riesgo y detección personalizada.

Los resultados del estudio transversal en pacientes con cáncer avanzado y los resultados de la revisión sistemática de estudios publicados que informan sobre la suplementación con vitamina D_2 o D_3 en pacientes con cáncer, apoyan la necesidad de VIDAFACT para proporcionar datos sobre la eficacia en términos de calidad de vida general con un ensayo clínico en pacientes con cáncer en cuidados paliativos.

Today we fight.
Tomorrow we fight.
The day after, we fight.
And if this disease plans on whipping us, it better brings a lunch, 'cause it's gonna have a long day doing it.
—Beaver, 2008

You need to spend time crawling alone through shadows to truly appreciate what it is to stand in the sun.
—Hick, 2014

ACKNOWLEDGMENTS

There are many people for whose assistance and support I owe a debt of gratitude.

My mother Julia, my father Benjamin, and my sister Rosa gave me their unconditional love and friendship, making me what I am today. And for that, I thank them immensely.

There are three people especially that I would like to acknowledge whose paths in life crossed mine and, consequently, defined the contents of this thesis.

Montse Rue, a friend deserving of special thanks, motivated me to make one of the two most important changes in my life so far, moving from working in epidemiological research in Barcelona, to working in clinical research and teaching biostatistics in Lleida. She encouraged to do the thesis, joining her research team to assess the impact of early detection and new adjuvant treatments in the evolution of the incidence and mortality of breast cancer in Catalonia. My contribution to this project is reflected in the first article of the thesis, but hers appears on every page, for which she provided her invaluable supervision.

Adriana Dusso, an Argentinian friend who came to Lleida from St. Louis four years ago, told me for the first time about the potential benefits of vitamin D in people with cancer, and encouraged me to make the second most important change in both, my life and this thesis. Thanks to her, I initiated and incorporated the study of the possible role of vitamin D in the quality of life for people diagnosed with advanced cancer in palliative care and with no possible curative treatment options. To be honest, it was not just conversations with Adriana that brought about the creation of this line of research, but also the union of this knowledge with the fact that my mother was

later diagnosed with stomach cancer with peritoneal metastases without options for either chemo or radiotherapy. I administered cholecalciferol to her on my own, since oncologists with whom I spoke always said there was not enough evidence to prescribe it. After less than one month my mother improved to the point of opting for chemotherapy. My contribution to this research is found in the last three articles of the thesis, while hers can be seen on every page devoted to vitamin D, each of which benefitted tremendously from her invaluable supervision.

Lastly, but in a more tender and personal way, I want to thank my mother, Julia Alonso, a strong woman who left me with a courageous example by not feeling sorry for herself even as she was fighting cancer in her own body. She fought to the final moments, being more concerned about others than herself. During those days I remember telling her "Cancer has many bad things but in this case, within the bad, it just so happens that not only do I work in medical research in a hospital, but I also have a friend who is an expert in vitamin D. This coincidence can enable many other cancer patients, in addition to Adriana's friends and mine, to benefit from supplementation with vitamin D, because I am planning to do a clinical controlled trial, so no one can say that there is no evidence". Though she'll never have the opportunity to read this paper or see the results of the clinical trial, this thesis, as I told her before her passing, is dedicated to her.

I also want to thank three people for their invaluable help and contribution to this thesis. First, Ester Vilapriñó, a friend who is one of the authors of the first article for helping me to estimate overdiagnosis by incorporating into the program Mathematica my estimations of incidence. And secondly, Dr Maria Nabal, a palliative care physician and friend whom I must thank all her support to the project, since without it, it would have been impossible to have carried out the study. And lastly, but by no means least, Dr Gemma Ariza, a rehabilitation physician and friend whom I must thank all her support to the project since her work is essential for observing the maximum beneficial effect of vitamin D.

I also want to thank, for always being there whenever I needed them, the rest of my friends and family, and especially Yolanda, Laura, Gemma, Miquel, Dave, Maria, Mireia, Silvia, Esther, Montse, Jana, Carles and Joan.

Finally, I would like to thank the anonymous people with advanced cancer in palliative care who have participated in the cross-sectional study.

CONTENTS

Part I

INTRODUCTION

1

BACKGROUND

Much of the recent debate on the early detection of breast cancer through mammography screening revolves around overdiagnosis, or the diagnosis of a condition that would cause neither symptoms nor death. Although screening tests can cause damage (such as pain and anxiety from mammographies and biopsies), this is usually transient. The consequences of cancer overdiagnosis and subsequent treatment lasts a lifetime. The surgical treatment involves risks from anaesthesia and surgical complications. Possible short-term side effects of adjuvant treatments include hair loss, neutropenic sepsis, hot flashes, vaginal dryness, and increased risk of fracture for patients receiving endocrine therapy. Possible long-term consequences include cardiovascular and respiratory complications if the patient receives radiotherapy. One unavoidable consequence for an individual diagnosed with cancer by a screening test is the decrease in quality of life, highlighting the need to quantify the amount of overdiagnosis associated with early detection by screening mammography.

If it is important to preserve quality of life in healthy women attending mammographic screening, then for patients with advanced cancer in palliative care, quality of life is of the greatest importance. Palliative care involves the prevention, improvement or the control of symptoms like asthenia, caquexia, functional limitation and autonomy loss. Given the multiple health benefits associated with normal vitamin D levels in healthy individuals, we decided to start a new line of research on vitamin D supplementation in advanced cancer. It includes a systematic review, a cross-sectional study and the design of a randomized controlled trial with the aim of assessing the efficacy of vitamin D_3 supplementation (cholecalciferol) in advanced cancer patients. Our objective is to provide scientific evidence of the effects of a non-costly treatment for patients receiving palliative care on their quality of life.

1.1 OVERDIAGNOSIS OF BREAST CANCER

In Western countries, mortality from breast cancer (BC) has shown a decreasing trend since 1990. In the US, the use of both screening mammography and adjuvant treatments have had a similar role in this reduction (Cronin 2006). Unfortunately, BC is still the most frequent cancer in women and the leading cause of death in women aged 35 to 64 (Ferlay 2004). In Spain, BC ranks third for malignant neoplasia in disability-adjusted life years lost, after lung and colorectal cancers.

One of the possible adverse effects of mammographic screening is overdiagnosis or detection of lesions that, had they not been detected, would have been silent throughout the woman's lifetime. Along with false positive and negative results, overdiagnosis is considered to be an adverse effect of screening. For an individual, since most people who are diagnosed are also treated, it is difficult to assess whether overdiagnosis has occurred.

Most of the inferences about overdiagnosis come from population-based studies. An evidence of overdiagnosis came from the long-term follow-up of the Malmo randomized trial of mammography screening, in which there was an excess of 115 (10%) detected breast cancers in the screened group 15 years after the trial was completed. Overdiagnosis has also been identified in chest x-ray screening for lung cancer. Long-term follow-up of the Mayo Clinic randomized trial of screening with chest x-rays and sputum cytology found an excess of 46 lung cancer cases in the screened group 13 years after the trial was completed, suggesting that 20-40% of lung cancers detected by conventional x-ray screening represent overdiagnosis. Overdiagnosis is also present in the high increase of new cases of prostate cancer observed following the introduction of the prostate specific antigen (PSA) screening test. Autopsies have also revealed a non-negligible prevalence of indolent tumors in people who died from other causes. Given all these evidences, a conference on preventing overdiagnosis is organized every year since 2013 by the National institutes of Health and the National Cancer Institute in the USA.

Screen-detected cancers have a higher probability of being slow-growing cancers. Some of the screen-detected cancers will not cause symptoms during a person's life. Although the concept of non progressive cancers may not seem plausible, basic scientists have found some biologic mechanisms that could explain the lack of progression. Some cancers outgrow their blood supply and are starved, others are recognized by the host's immune system and are successfully contained, and some are indolent tumors. In fact, the American Society

of Medical Oncology (ASCO) has started a debate to change the name of the ductal carcinoma in situ and the high-grade prostatic intraepithelial neoplasia. These are premalignant conditions that should not be labeled as cancers or neoplasia, nor should the word 'cancer' be in the name. They propose to reclassify such conditions as indolent lesions of epithelial origin (IDLE) (Esserman, 2013).

The estimates of overdiagnosis in breast cancer are highly variable depending on the study design and methodology used. Thus, Paci et al estimated it at 4.6% (Paci 2006), whereas Zahl et al estimated that it affects a third part of the tumours detected in women aged 50 to 69 (Zahl 2008). A literature review in 2012 by Puliti et al estimated overdiagnosis between 1 and 10% (Puliti 2012). The methodology used to estimate overdiagnosis varies widely, as does their estimated magnitude. Randomized controlled trials have low risk of bias but limited generalizability. Ecological and cohort studies are limited by data quality, follow-up length and the potential for population level confounders. Pathological or imaging studies are based on examining overdiagnosis resulting from non-progressive disease and not competing mortality and are limited by assuming that pathological or imaging characteristics were directly and strongly correlated with cancer related morbidity and mortality. Finally, mathematical models require complex mathematical equations simulating the natural (and unknown) course of screen detected cancer, obtaining results in a shorter time.

When randomized clinical trials are difficult to undertake, mathematical models that use all available data from either observational studies or clinical trials or cancer registries may be a good alternative. Mathematical models have been used by several research groups supported by the National Cancer Institute in the US and the Cancer Intervention and Surveillance Modeling Network (CISNET) (CISNET 2008). One of these research groups was led by Sandra Lee and Marvin Zelen who together developed a very detailed analytical model (Lee 2008). We have used this model to estimate the expected number of breast cancer cases in the absence of overdiagnosis and also to assess the excess of cases that can be attributed to the use of mammography for the early detection of breast cancer in relation to the observed breast cancer incidence.

1.2 QUALITY OF LIFE IN ADVANCED CANCER

Palliative care is defined as the discipline whose aims are to minimize symptoms, to relieve suffering and to work to achieve the best possible quality of life, when the disease cannot be cured. In this context, to minimize the toxicity of any treatment is a priority.

Asthenia or cancer-related fatigue is the most frequent symptom in patients treated by palliative care professionals, with a global prevalence of 90% in the early stages of the disease. Fatigue cannot be easily diagnosed because it is usually masked by other symptoms such as pain, nausea or shortness of breath. It will only be visible to patients and physicians after the resolution of these problems. It is a symptom that interferes largely on the autonomy of individuals, the basic activities of daily life and has a huge impact on emotional status and the social/family environment.

In addition to the difficulties in detecting fatigue as a symptom, the assessment of its intensity is a challenge. Although there are tests that measure the precise level of physical strength, fatigue is a symptom with a very important emotional component related to the management of losses. To adequately address these problems, specific questionnaires have been developed, which allow clinicians to measure the perception of fatigue and its impact on quality of life (Stewart 2006 , Lane 2005).

Another open question is related to the choice of the most appropriate treatment. Although the pathogenesis of cancer-related fatigue is unclear, it is known that it is a multi-causal phenomenon. Physiological and biochemical disorders have been identified which are directly associated with tumor progression. In addition, there are serious adverse effects resulting from the specific treatment of cancer; factors related to physical and psychological stress; anemia, lack of exercise, chronic pain, uncontrolled severe symptoms. All of them are often present in most chronic diseases.

Among the multiple interventions studied, the ones that seem to offer promising results and support a multimodal approach are: drug therapy, exercise and nutritional interventions (Davis 2005). However, for patients in palliative care, specific recommendations are scarce.

Exercise, framed within functional physiotherapy, must be customized and adapted to the limitations and potential of each person. Its objective is not to achieve the highest level of activity, but to improve and maintain physical resistance to keep muscle reserves.

Several pharmacological interventions have been proposed including erythropoietin to control anemia with controversial results; corticoids which convey a feeling of euphoria resulting in little or no actual improvement of physical strength; progestagens which stimulate the appetite and increase weight (since fatigue is often associated with malnourishment); hormonal interventions as megestrol-acetate with non relevant benefits; psycho stimulants as methylphenidate administered with some rapid success in both HIV and cancer patients (Lower 2009, Martin 2001 Kerr 2012). However, these drugs elicit adverse effects that impede their use in patients with high blood pressure, brain tumors or arrhythmias.

The detection of symptoms of hypogonadism in patients with HIV or cancer caused by their treatment, which result in fatigue and loss of muscle mass, have been resolved with testosterone replacement to correct low testosterone levels. Additional medication includes an inhibitor of acetyl cholinesterase used to treat Alzheimer's patients, sympatheticmimetic agents and fluoro-cortisone, as well as L-carnitine, melanin-stimulant hormone, monoclonal antibodies against TNF alpha, or COX 1 and COX2 inhibitors, each of which was directed to one or a few components of the multifactorial pathogenesis of fatigue.

In view of the obvious urgent need to develop new evidence based interventions for palliative care cancer patients, and based upon: 1) the strong epidemiological relationship between vitamin D deficiency and the high risk of mortality for all causes in the general population (Adams 2010); 2) the high frequency of vitamin D deficiency in cancer patients, and 3) the anti-cancer, anti-aging, anti-pain, immunomodulatory, and the protective renal, cardiovascular and neuro-muscular properties of a normal vitamin D status (Adams 2010, Boullion 2008), we propose that the simple, non-costly, and safe correction of vitamin D deficiency in patients in palliative care could markedly improve their quality of life. Indeed, in recent years, it has become apparent that the health benefits of a normal vitamin D endocrine system extend beyond the maintenance of normal calcium and phosphate homeostasis and a healthy skeleton. In the general population, vitamin D deficient individuals are at a higher risk of mortality for all causes, including several disorders of aging such as cardiovascular disease, hypertension, diabetes, renal lesions, cancer, and autoimmune disease (Adams 2010, Boullion 2008).

Although the strongest epidemiological association does not constitute a proof of causality, the clear delineation of the multiple mechanisms underlying vitamin D prosurvival actions support our hypothesis. That is, that the implementation of inexpensive strategies to correct vitamin D deficiency in patients in palliative care may prove

cost-effective in preventing the onset and/or attenuating the progression of several of the multifactorial etiologies of cancer-related fatigue caused by defective vitamin D control of: 1) cell growth causing hyperproliferative disorders, genomic instability, TACE-driven metastasis, exacerbated growth and immune escape; and accelerated progression of cancer lesions (Adams 2010; Grotsky 2013; Dusso 2010; 2) DNA repair mechanisms causing age-associated disorders and resistance to therapy in cancer (Gonzalez-Suarez 2011; Grostky 2013); 3) muscular weakness and impaired neuromuscular functions (Boullion 2008, Napoli 2010); 4) musculoskeletal pain derived from cancer treatment (Rastelli 2011); 5) the immune system causing increased antigenicity in antigen presenting cells, reduced content of T regulatory lymphocytes, systemic inflammation and multiple organ damage, as well as a higher propensity for autoimmune disorders (Adams 2010; Boullion 2008); 6) the integrity of the FGF23/klotho responsible for the anti-aging properties of klotho in the kidneys, in protecting the vasculature from atheromatosis and calcification, and as a tumor suppressor and protector from the onset of resistance in cancer treatment (Haussler 2012; Lim 2012, Wolf I 2008); 7) the renin-angiotensin system to prevent hypertension, renal and cardiovascular damage due to excessive oxidative stress (Li 2010, Zhang 2011); 8) acquisition of atherotrombotic phenotype of circulating monocytes-macrophages and increased severity of atherosclerotic lesions (Oh 2009); 9) podocyte function to protect from proteinuria and proteinuria-induced cardiovascular lesions (He 2011; DeBoer 2007).

Importantly, the multiple health disorders and the increased risk of mortality associated with vitamin D deficiency are unrelated to abnormalities in serum levels of the vitamin D hormone, $1,25-dihydroxy-vitaminD$ (1,25D). Instead, the low serum $25-hydroxyvitaminD$ (25D) levels of vitamin D deficiency results in a lower local conversion of 25D to 1,25D, causing defective autocrine/paracrine vitamin D actions. For example, the simple correction of vitamin D deficiency in African-Americans with an enhanced propensity to tuberculosis outbursts, allows the local conversion of 25D to 1,25D in monocyte-macrophages to induce the synthesis of cathelicidin to kill the mycobacterium.

Similar actions are expected to occur locally upon correction of vitamin D defficiency in tumoral or metastatic cancer cells to suppress further growth, or in multiple cell types attenuating inflammatory responses, enhancing muscular strength, reducing oxidative stress or DNA damage, inducing anti-aging activities with minimal repercussions in systemic calcium homeostasis, thereby reducing the risks of potential vitamin D toxicity. The additive effects of these pleiotropic vitamin D actions should safely improve the quality of life of patients

in palliative care.

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2 THIS THESIS

2.1 HYPOTHESIS

- Overdiagnosis of breast cancer in women attending breast cancer screening is not negligible and leads to overtreatment.
- The research with cholecalciferol or ergocalciferol in cancer is scarce and suffers from the lack of randomized controlled trials measuring efficacy.
- Perceived health-related quality of life, fatigue and physical performance of patients with advanced cancer is associated with 25-hydroxyvitamin D serum levels.
- Patients with advanced cancer in palliative care could benefit from supplementation with vitamin D.

2.2 OBJECTIVES

1. To assess the magnitude of overdiagnosis attributable to mammography screening for breast cancer.
2. To perform a systematic review of the published literature on treatment with supplements of inactive vitamin D (D_2 or D_3) in cancer patients.
3. To assess the association between serum levels of 25-hydroxyvitamin D and patient-perceived health-related quality of life, fatigue and physical perfomance.
4. To design a randomized controlled trial to assess the efficacy of a supplemental therapeutic modality with vitamin D_3 designed to improve the patient perceived health-related quality of life.

2.3 BRIEF SUMMARY OF THE RESEARCH ARTICLES OF THIS THESIS

The first article in *Chapter 2* is titled *Breast cancer incidence and overdiagnosis in Catalonia (Spain)*. The aims of this study were to model invasive breast cancer incidence trends taking into account reproductive and screening data, and to quantify the extent of breast cancer overdiagnosis by screening mammography using mathematical models. It was published in *Breast Cancer Research*.

The second article in *Chapter 3* is titled *Outcomes reported from supplemention with vitamin D (cholecalciferol or ergocalciferol) to adult cancer patients. A systematic review*. The aim of this review is to identify and summarize all outcomes published in observational and experimental clinical studies reporting the results obtained from the supplementation of cancer patients with cholecalciferol or ergocalciferol. It includes all adult patients with cancer at any stage. It has been sent for consideration for publication to a peer-reviewed journal.

The third article in *Chapter 4* is titled *Vitamin D deficiency and its association with fatigue and quality of life in advanced cancer patients under palliative care. A cross-sectional study*. The aim of this study was to assess the relationship of Vitamin D deficiency with health-related quality of life issues, fatigue and physical functioning in advanced cancer patients. It is under peer-review in *Palliative Medicine*.

The fourth article in *Chapter 5* is titled *The effect on quality of life of vitamin D administration for advanced cancer treatment (VIDAFACT study): protocol of a randomised controlled trial*. The primary aim of the protocol are to evaluate the efficacy of the administration of vitamin cholecalciferol to enhance patient-reported HRQoL. The secondary aims include: (1) To evaluate the efficacy of the administration of vitamin D3 for enhancing physical performance, decreasing perceived fatigue and achieving serum levels of 25(OH)D above 30 ng/mL; (2) To evaluate the effect on tumour biomarkers; (3) To explore the relationship between vitamin D treatment compliance and 25(OH)D levels; (4) To explore the relationship between 25(OH)D levels and renal function; (5) To explore the dose–response relationship in the group of patients with vitamin D3 for the main outcome; (6) and to assess the cost utility of the proposed administration of vitamin D3. It was published in *BMJ Open*.

Part II

ARTICLES

3

BREAST CANCER INCIDENCE AND OVERDIAGNOSIS IN CATALONIA (SPAIN)

Published in:
Martinez-Alonso M, Vilaprinyo E, Marcos-Gragera R, Rue M. Breast Cancer Research 2010, 12:R58

This published article estimates breast cancer incidence trends and, particularly, the overdiagnosis attributable to the use of mamography as an early detection screening tool to be applied in asymptomatic women.

The overdiagnosis occurs when early detection finds a tumor that would not have been diagnosed symptomatically. Among the factors that could explain the overdiagnosis are the existence of competing causes of death that act on the latency of tumors as well as a potential fraction of tumors that remain encapsulated or even regress over time.

Our estimates are limited to invasive breast cancers and do not include the ductal carcinoma in situ type, a pre-cancerous or non-invasive cancerous lesion of the breast, classified as Stage 0, that rarely produces symptoms or breast lumps and is usually detected through screening mammography.

We used probability models based on the models developed by Lee and Zelen (LZ) to estimate overdiagnosis. These models include the density functions and the cumulative probability functions of the phenomena involved in the incidence of breast cancer. These models take into account the lead time that results when breast cancer is diagnosed earlier by using a screening tool. Lead time is defined as the length of time between the early detection of an asymptomatic tumor and its usual clinical (symptomatic) presentation. The population included in the study are Spanish adult women 40 to 80 year old. Different data sources, for cohorts born between 1930 and 1970, were used.

To estimate the incidence of invasive breast cancer we used a Poisson regression model with explanatory variables age at diagnosis and characteristics of the cohort, like completed fertility rate, percentage of women using mammography at age 50, and year of birth. The year of birth acts as a proxy of the remaining cohort characteristics for which we do not have data over time, like use of hormone replace-

ment therapy, use of oral contraceptives, obesity, diet or health awareness. This model was also used to estimate the baseline incidence in the absence of screening. It applies a probabilistic model to estimate the expected incidence of breast cancer based on the reported mammography use in the Catalan health surveys. The difference between the observed and expected cumulative incidences provides an estimate of overdiagnosis of invasive breast cancer associated to mammography in Catalonia.

Martinez-Alonso et al. Breast Cancer Research 2010, 12:R58
http://breast-cancer-research.com/content/12/4/R58

Breast Cancer RESEARCH

RESEARCH ARTICLE Open Access

Breast cancer incidence and overdiagnosis in Catalonia (Spain)

Montserrat Martinez-Alonso[1,2†], Ester Vilaprinyo[3†], Rafael Marcos-Gragera[4,5], Montserrat Rue[1,2*]

Abstract

Introduction: Early detection of breast cancer (BC) with mammography may cause overdiagnosis and overtreatment, detecting tumors which would remain undiagnosed during a lifetime. The aims of this study were: first, to model invasive BC incidence trends in Catalonia (Spain) taking into account reproductive and screening data; and second, to quantify the extent of BC overdiagnosis.

Methods: We modeled the incidence of invasive BC using a Poisson regression model. Explanatory variables were: age at diagnosis and cohort characteristics (completed fertility rate, percentage of women that use mammography at age 50, and year of birth). This model also was used to estimate the background incidence in the absence of screening. We used a probabilistic model to estimate the expected BC incidence if women in the population used mammography as reported in health surveys. The difference between the observed and expected cumulative incidences provided an estimate of overdiagnosis.

Results: Incidence of invasive BC increased, especially in cohorts born from 1940 to 1955. The biggest increase was observed in these cohorts between the ages of 50 to 65 years, where the final BC incidence rates more than doubled the initial ones. Dissemination of mammography was significantly associated with BC incidence and overdiagnosis. Our estimates of overdiagnosis ranged from 0.4% to 46.6%, for women born around 1935 and 1950, respectively.

Conclusions: Our results support the existence of overdiagnosis in Catalonia attributed to mammography usage, and the limited malignant potential of some tumors may play an important role. Women should be better informed about this risk. Research should be oriented towards personalized screening and risk assessment tools.

Introduction

Breast cancer (BC) incidence rates in women have been increasing steadily in the 1980 s and 1990 s in many countries. Time trends in the incidence of breast cancer have been influenced by different factors: changes in reproductive patterns, the introduction of screening mammography, obesity trends, hormone replacement therapy (HRT), oral contraceptive use and better health awareness [1-10]. In Europe, BC incidence increased in all countries, with or without national screening programs [6]. In Spain, where BC incidence is lower than the European average, incidence rates have increased since 1973, with a more marked rise during the 1990 s [11] in parallel with the dissemination of mammography, both opportunistic and publicly organized screening programs. In Catalonia (Spain), the annual percentage change between 1980 to 1984 and 1995 to 1999 was 2.2% [12] and new cases of female BC were estimated at 4,700 in the year 2008. This quantity represents 30% of all cancer diagnoses in women.

Screening increases incidence rates in three ways [13]. First, there is an immediate rise in incidence, due to the early diagnosis of prevalent asymptomatic cancers [14,15]. Second, age at diagnosis decreases as a result of the lead time introduced by screening (estimated as two to four years) [16]. Third, screening may cause overdiagnosis when it detects tumors which would never have been diagnosed during a lifetime without screening because of the lack of progressive potential or death from other causes [17-21].

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Estimates of overdetection of invasive cancer may be affected by important biases. Biesheuvel *et al*. mentioned 1) differences in the underlying breast cancer risk between screened and unscreened populations, 2) contamination of intervention and control groups, 3) screening in the control group after the intervention period ends, and 4) inadequate allowance for lead-time [22]. It seems that the older trial data tend to provide lower estimates of overdiagnosis, whereas the more recent observational data tend toward higher estimates. Since no decline in interval cancer rates has been observed [23] part of the overdiagnosis increase may be related to an increase in the sensitivity of mammography (both for cancers that will progress and for tumors of limited malignant potential).

Mathematical modeling may overcome some of the previous mentioned biases. In the US, Holford estimated the contribution of screening to the upward trend in BC incidence using log-linear models for age, period and birth cohort (APC) [24]. Holford's models also provided background estimates of trends that might have been expected as a result of the continuation of historical increases in the rates. The Cancer Intervention and Surveillance Modeling Network (CISNET) used the background estimates as inputs for modeling the impact of screening and adjuvant treatments on BC mortality trends [25,26].

The interest in assessing the impact and cost-effectiveness of breast cancer early detection programs in Catalonia (Spain) led us to work with mathematical models developed by Lee and Zelen within the CISNET [27,28]. The aims of this study are 1) to use reproductive and screening data to model invasive BC incidence trends and to obtain background estimates of invasive BC incidence and 2) to use the Lee and Zelen mathematical models to quantify the extent of overdetection of invasive BC related to screening.

Materials and methods

Setting

In Spain there is a National Health System (NHS), financed primarily by taxes, which provides universal and free health coverage, including early detection of breast cancer. Catalonia is an autonomous region of Spain which has approximately one sixth of the Spanish population. The Catalan Breast Cancer Screening Program (BCSP) started gradually, at the beginning of the 1990 s, providing biennial mammography screening tests to women 50 to 64 years old. Since the year 2000, women older than 64 are kept in the program until the age of 69. Before the start of and in addition to the BCSP, there has also been a certain degree of opportunistic breast cancer screening done in the public and private health care sectors. In the 1994 Catalan Health Survey, when most of the screening in Catalonia was opportunistic, rates of screening mammography were 43% in women aged 40 to 49 years and 27% in women aged 50 to 64 years [29]. In 2004, 61.2% of the invited women participated in the BCSP and 75.7% either participated in the BCSP or reported that they had received recent mammograms (non-published BCSP data).

Data

To model invasive breast cancer incidence rates in Catalonia, age and period specific incidence data were obtained from the Girona and Tarragona population-based cancer registries in Catalonia (both provinces representing 18.5% of the total Catalan population and covering either urban and rural areas). The Girona and Tarragona provinces have around 750,000 and 800,000 inhabitants, respectively. Data from Girona was provided directly by the Girona Cancer Registry and data from Tarragona was downloaded from the International Agency for Research on Cancer registries (IARC) [11]. Incidence data were available for calendar years 1980 to 1989 and 1991 to 2004 for Girona and 1983 to 1997 for Tarragona. Given that the breast cancer incidence rates in the Girona and Tarragona registries are similar [30], both data sources were combined. Numerators for the incidence rates were calculated adding the number of incident cases from both registries by age and calendar year. Denominators were calculated adding the number of women at mid-calendar year, in the Girona and Tarragona provinces, and were obtained from official census population data [31]. We have assumed that the estimated incidence rates were representative of the breast cancer incidence in Catalonia. Ductal carcinoma in situ (DCIS) has not been included in the analysis.

The research protocol was approved by the institutional review board and ethics committee of the Hospital Universitari de Bellvitge (Barcelona) which waived the need for informed consent.

Breast cancer incidence models

We modeled the **observed incidence** of invasive BC for Catalan women aged 25 to 84 during the time period 1980 to 2004 using an age-cohort model that incorporated cohort characteristics like intensity of mammography utilization and fecundity rate. We did not introduce a period effect because screening mammography was disseminated gradually in our country. We used this model to estimate the **background incidence** of BC under the assumption of no screening. Then, using a probabilistic model that takes into account background incidence, competing risks, distribution of sojourn time in preclinical state, sensitivity of mammography and the dissemination of screening in Catalonia, we estimated the increased age-specific incidence due to lead time

(**expected incidence**). Finally, we estimated **overdiagnosis** comparing the observed and expected cumulative incidences, by cohort of birth. In the following sections there are the models' details.

Observed incidence model

Observed incidence rates were fitted using an age-cohort model where the cohort effects were split into three components. The first component refers to the fecundity of the cohort and was measured using the cohorts' completed fertility rate (CFR). CFR is the average number of births per woman up to the end of the childbearing years [32]. There is evidence that high parity is protective of breast cancer independent of ages at first and last full term pregnancies [33]. The second component refers to the intensity that mammography was used for each specific cohort and was measured as the proportion of women who were having periodic mammograms for early detection at age 50 (PM50). This value was obtained from a previous work of modeling mammography dissemination in Catalonia (see the details in Appendix A in Additional file 1) [34]. Finally, the third component refers to the remaining cohort characteristics once fecundity and mammography use have been taken into account and for which we do not have data over time, like use of HRT, use of oral contraceptives, obesity, diet or health awareness. The third component has been included in the model as the year of birth of the cohorts.

Our BC incidence model uses age, CFR, PM50 and year of birth to estimate the number of BC incident cases by age and cohort of birth. It assumes a Poisson distribution of the incident cases and takes into account the exposed population. We used fractional polynomials to describe the age and cohort effects in order to increase the exibility of conventional polynomial models and avoid undesirable artifacts of high-order curves (see Appendix B in Additional file 1 and reference [35] for more detail). Since mammography use (PM50) and CFR had opposite trends in most of the studied periods, and PM50 was strongly associated with BC incidence, we decided to include CFR in the model as an *offset* with the coefficient -0.15. This value was obtained from the literature and indicates a relative risk of BC equal to 0.85 for each child born [1,2,36].

Goodness of fit was assessed using the deviance and the likelihood ratio test with respect to the saturated model. Overdispersion of the Poisson model was assessed. Plots of residuals versus fitted values and predictors were assessed to check for lack of fit related to the scale of predictors (data not shown). Confidence intervals of the predicted values were obtained using the delta method and bootstrap.

Background incidence model

BC incidence in absence of screening, by cohort of birth, was derived from the BC observed incidence model by considering that the proportion of women having periodic mammograms at age 50 (PM50) was zero. Confidence intervals for background incidence were obtained using the delta method and bootstrap.

Expected incidence and overdiagnosis estimation

Using the probabilistic model developed by Lee and Zelen (LZ) for the CISNET [28] we estimated expected BC incidence if women in the population had used mammography as they reported in health surveys, and overdiagnosis was zero. This estimate takes into account the lead time that results when breast cancer is diagnosed earlier. Then the difference between the observed and expected incidence provided an estimate of overdiagnosis. The steps were the following (Figure 1):

1. We considered all the scenarios that assumed a) 100% of women starting screening mammography at age z with $40 \le z \le w_{\max}$, where $w_{\max}$ is the highest age attained by each cohort and b) the periodicity of the exams was annual or biennial. For instance, for cohort 1950, $w_{\max}$ was 54, then z took 15 different values. Therefore, for this cohort 30 different scenarios were computed (15 with annual screening and 15 with biennial screening).

2. We used the LZ model to estimate the number of breast cancer incident cases by age and cohort of birth in each of the scenarios mentioned in step 1, assuming that each cohort had 100,000 women at birth. See the equations in Appendices C and D in Additional file 1 and [28,37-40] for more detail.

3. We considered the dissemination of mammography use in Catalonia by age and birth cohort in order to obtain the scenario that best represents the real pattern of mammography use for each cohort. Weighting the estimates obtained for each scenario in step two by the pattern of mammography use, we obtained the estimated number of incident cases by age and birth cohort (see Appendix B in Additional file 1).

4. For each cohort we obtained the expected cumulative incidence (per 100,000 women at birth) adding the incident cases obtained in step three. We represent this estimate by CI_e.

5. We estimated the observed cumulative incidence by 100,000 women at birth (CI_o) multiplying the observed age-specific incidence rates by the probability of being alive at each age, and adding up all these values.

Finally the estimates of overdiagnosis by cohort of birth were obtained using the formula:

$$100 \times \frac{CI_o - CI_e}{CI_e}$$

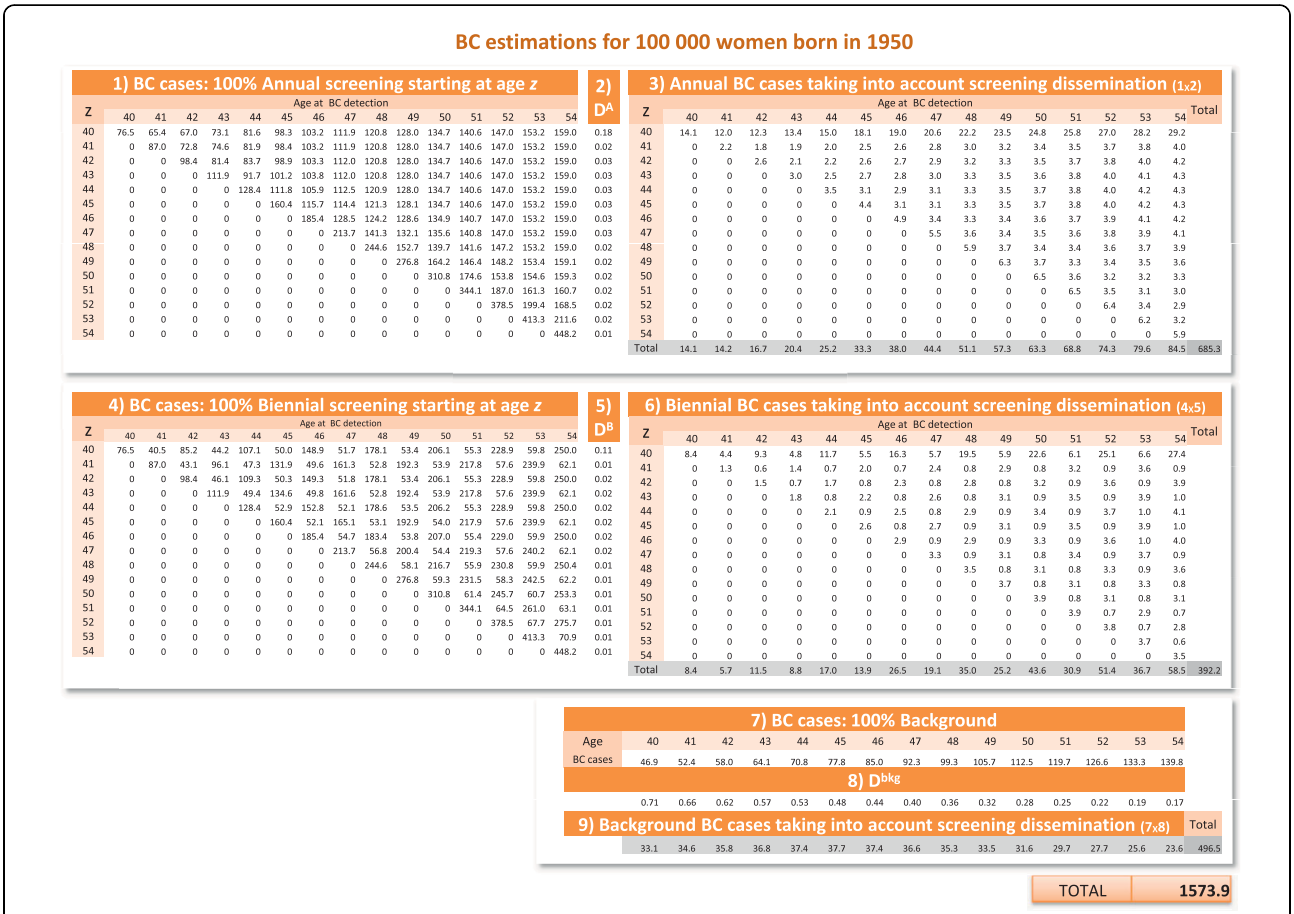

Figure 1 Steps for estimating overdiagnosis for cohort 1950. See Appendix E.1 in Additional file 1 for a detailed description.

Appendix E in Additional file 1 shows the calculation of overdiagnosis for the cohort born in 1950 as an illustrative example.

The steps taken to obtain confidence intervals of the overdiagnosis estimates are described in Appendix E.2 in Additional file 1.

Sensitivity of the overdiagnosis estimates to changes in relevant parameters

We obtained new estimates of overdiagnosis by modifying the following parameters:

1. Mean sojourn time in pre-clinical state (α). In the LZ model α takes values in the range of two to four years, depending on age. We estimated overdiagnosis when α = 1 and when α = 5 for all ages. These scenarios would represent tumors growing faster or slower than in the LZ model, respectively.

2. Mammography sensitivity (β). In the LZ model β varies from 0.35 to 0.8, depending on age of the woman and year when mammography was performed. We estimated the overdiagnosis assuming β = 0.9 for all ages.

3. Repeat mammography behavior. Since the distributions of periodicity of mammograms in Catalonia were quite stable along different ages and calendar years, we obtained new estimates of overdiagnosis in the most extreme situations:

a. 1994 Health Survey for the age-group 40 to 49 years (annual = 0.76, biennial = 0.21, irregular = 0.04).

b. 2006 Health Survey for ages from 60 to 69 years (annual = 0.52, biennial = 0.35, irregular = 0.13).

Software

The Stata SE/10 statistical package was used to fit the Poisson model for BC incidence, to bootstrap the residuals and to obtain confidence intervals [41]. The Grid Mathematica v6 program was used to apply the stochastic LZ model, to estimate the number of BC incident cases under different screening scenarios, and to estimate overdiagnosis [42].

Results

Figure 2 shows the trend over time of the completed fertility rate (CFR) (2a) and of the proportion of women receiving periodic mammograms at age 50 (PM50) (2b), two of the cohort variables used to model BC incidence.

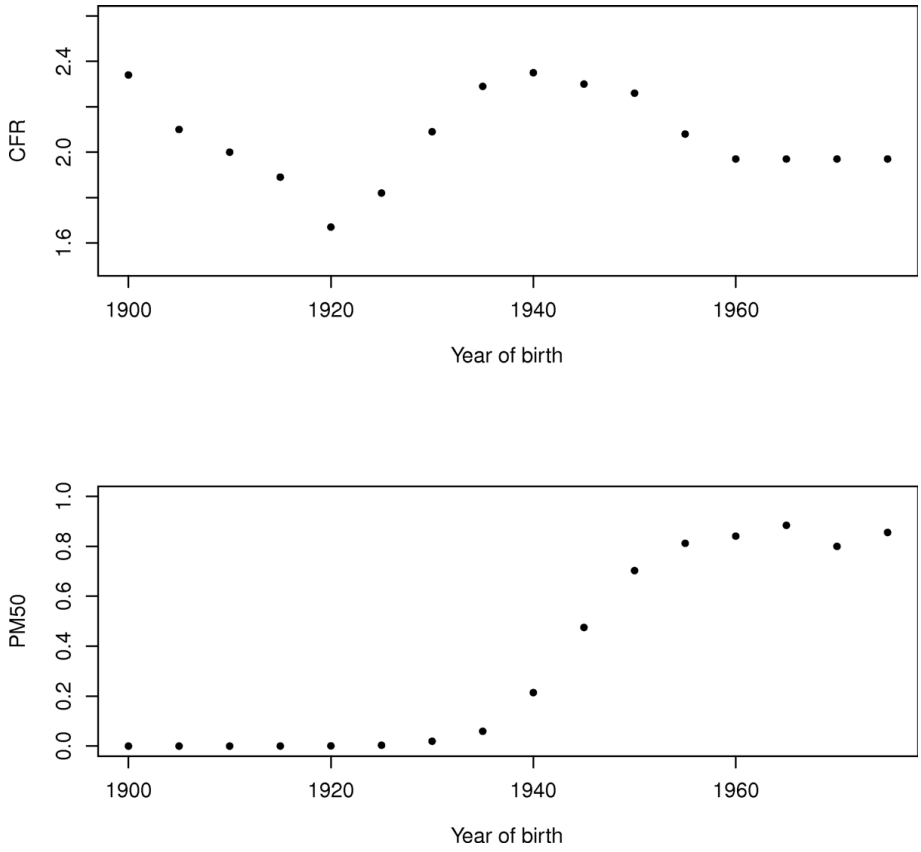

Figure 2 Completed fertility rate (CFR) and proportion having periodic mammograms at age 50 (PM50).

Figure 2a shows that CFR decreased for women born between 1900 and 1920 and then increased from 1920 to 1940, reaching a maximum of 2.35 children for women born in 1940. After, the CFR decreased again. Figure 2b shows a big increase in mammography usage from 1935 to 1955. For a woman born after 1955 the values of PM50 stabilized at approximately 0.8. It is important to note that for women born between 1940 and 1955 we observed both a decrease of CFR and an increase of PM50.

Table 1 shows the equation, the estimated coefficients and standard errors of the BC incidence model. Fractional polynomials selected powers two and three for age, lineal for year of birth and power 0.5 for PM50. Independent variables were centered with respect their means. The model coefficients indicate that incidence increased with age, year of birth and exposure to periodic mammography. The square root effect of PM50 on BC incidence indicates that the impact of mammography use in BC incidence attenuated as PM50 increased. The effect of fecundity on BC incidence was considered inverse and constant overtime.

The observed BC incidence rates and the estimation provided by the model can be observed in Figure 3 grouped by year of birth. There was agreement between observed and predicted values. Data shows an increase in BC incidence, especially in cohorts born from 1940 to 1955. The biggest increase of BC incidence was observed for ages 50 to 65 years, where the lowest BC incidence rate was less than half of the highest. The slopes of the estimated rates for the oldest cohorts were nearly parallel but we observed increasingly steeper slopes for the 1935 and younger cohorts.

Table 1 Breast cancer incidence model; Catalonia 1980 to 2004

	Coef.	Std. error	*P*-value
Age_1	-38.8418	1.0854	< 0.001
Age_2	0.0005	0.0002	0.002
$PM50_1$	0.6250	0.9878	< 0.001
YB_1	0.0111	0.0026	< 0.001
Constant	-6.0626	0.0156	< 0.001

The dependent variable is the number of observed incidence cases. The model has an offset, which is a term with coefficient constrained to 1. offset = log(exposed) 0.15 CFR, $Age_1 = (age/10)^{-2}$ - 0.0331, $Age_2 = (age/10)^3$ - 166.375, $PM50_1 = PM50^{0.5}$ - 0.4342, YB_1 = year-of-birth-1937.5. CFR: completed fertility rate, PM50: proportion of women who were having periodic mammograms for early detection at age 50. Deviance = 482.53. The expected number of incident cases, *E*(*I*), can be obtained using the equation: $E(I) = \exp(-6.0626 - 38.8418\ Age_1 + 0.0005\ Age_2 + 0.6250 PM50_1 + 0.0111 YB_1 + \text{offset})$.

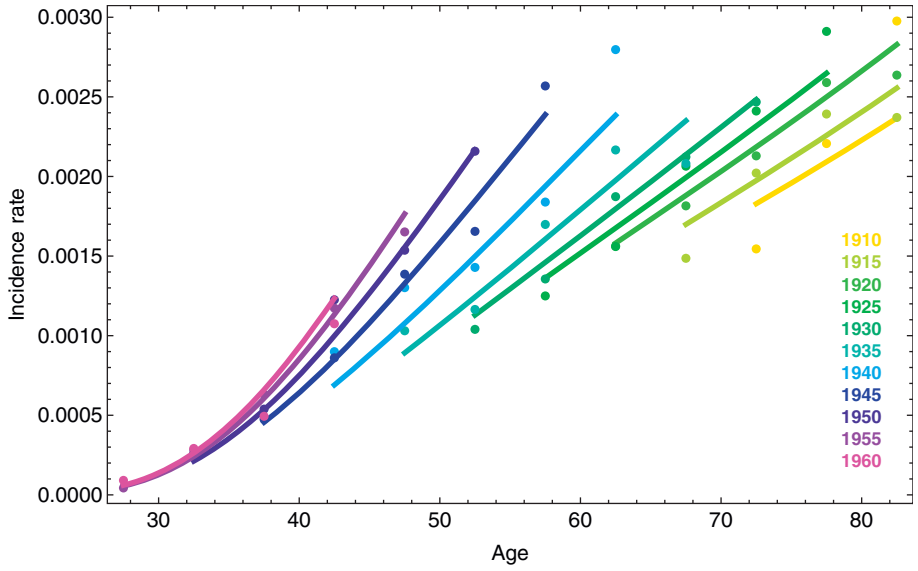

Figure 3 Observed breast cancer (BC) incidence rates per 100,000 women (points) and the fitted model (lines). Each color represents a cohort of birth.

Figure 4 shows the observed (dots), estimated (blue dashed line) and background incidence rates for cohorts 1935, 1940, 1945 and 1950 (purple line). Confidence intervals correspond to the bootstrap method and show narrow estimations (intervals obtained by the delta method were slightly narrower). Differences between background and screening scenarios were insignificant for woman born in 1935 or before (data not shown) and increasingly higher for woman born later. This provided the first clue to the magnitude of overdiagnosis due to screening.

Figure 5 presents the number of incident BC cases that would be obtained from a cohort of 100,000 women at birth in three different situations. The dashed line indicates the number of cases under the background incidence scenario and represents a situation of no mammography use. The solid line indicates the number of cases that would be diagnosed if mammography had been used as reported in the Health Surveys. These estimates were obtained by applying the LZ model to the background incidence. The increase in incidence with respect to the background is due to early diagnosis. Dots represent the number of observed cases for 100,000 women at birth and have been obtained from the observed incidence rates and probabilities of survival. In the absence of overdiagnosis, the dots would appear close to the solid line. The increasing distance between the observed and expected values by cohort of birth indicates that overdiagnosis has augmented over time.

Table 2 shows the overdiagnosis estimates and confidence intervals for cohorts born between 1935 and 1950. These estimates have been obtained by comparing cumulative incidences from 40 years of age to the last observed age in each cohort. Overdiagnosis estimates vary from 0.4%, 95% CI (-8.8%, 12.2%) for the 1935 cohort to 46.6%, 95% CI (22.7%, 85.2%) for the 1950 cohort.

Table 3 shows the results obtained after performing a sensitivity analysis for the overdiagnosis estimates. The largest change in overdiagnosis was observed when modifying mean sojourn time in the pre-clinical state (α). A pattern of mammography use caused a small change in overdiagnosis (less than a 5% change between the two extreme scenarios). Finally, the mammography sensitivity caused changes of around 1.5% in the overdiagnosis estimation.

Discussion

Principal findings

Breast cancer incidence in Catalonia has increased during the twentieth century with a more marked rise in cohorts born from 1940 to 1950, who were 30 to 40 years old at the beginning of the 1980 s. The progressive dissemination of mammography in Catalonia was significantly associated with this increase, once age and other cohort characteristics were considered. Our estimates of overdiagnosis ranged from 0.4% for women born in 1935 to 46.6% for women born in 1950.

Comparison with other studies

Incidence trends

Botha *et al*. studied breast cancer incidence and mortality trends in 16 European countries until the

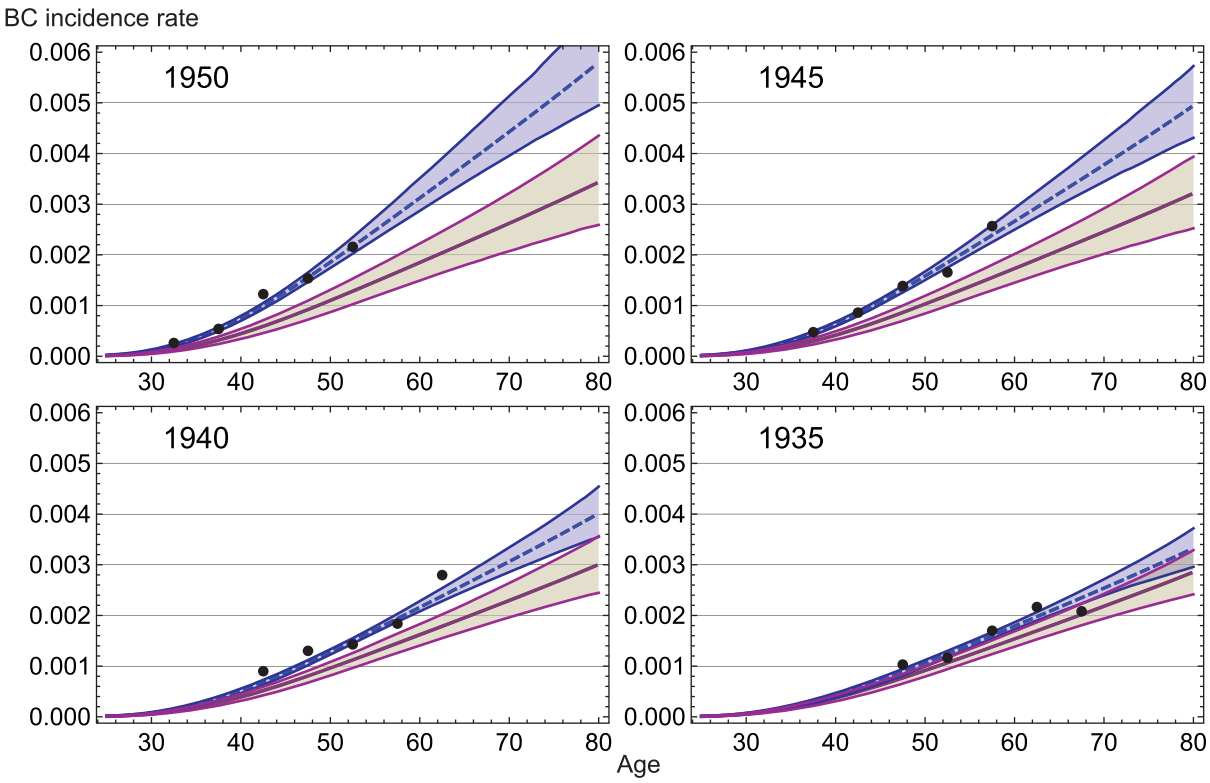

Figure 4 Breast cancer (BC) incidence model for *screening* and *background* scenarios. Each plot shows the results for cohorts born in 1935, 1940, 1945 and 1950: observed BC incident rates per 100,000 women (points), model with (dashed blue line) and without (purple line) screening. Confidence intervals were obtained using bootstrap.

mid-1990 s. Increases in incidence occurred in all countries, with or without national screening programs and, according to the authors, were consistent with changes in the risk factors [6]. In the USA, Holford *et al*. also found an increased trend with a peak in the mid-1980 s, when screening began to be more aggressively promoted [24].

In Spain, Pollan *et al*. studied the trend over time of the age-adjusted incidence rate of invasive breast cancer. Incidence increased steadily during the 1980 s and 1990 s and it appeared to decline in 2000 to 2004 in the Spanish provinces were screening had achieved full coverage of the target population in a short time period [43]. In Catalonia, where dissemination of screening took longer, the change in the age adjusted incidence trend was not observed.

In contrast to the previous studies, our incidence model was not only designed to assess the trend of breast cancer incidence over time but to obtain an estimate of the background incidence and overdiagnosis. Our results show a dramatic increase of age-specific incidence rates in cohorts born after 1940 associated to the intensity of mammography use in our region.

Overdiagnosis estimates

Overdiagnosis or overdetection estimates range from negligible [15,44] or low [45-48] to moderate [22,49-51] and high (50% or more) [14,52-55]. Some of the studies did not account for lead time bias or for decreases in incidence in older age groups no longer screened [44,46].

A review of the eight randomized trials of mammography found that in recent trials in which the control group was not offered screening, an excess incidence of breast cancer remained after many years of follow-up. In those trials in which the control arm was offered screening, there was no evidence of overdiagnosis, although there was a possible shift from invasive to *in situ* disease [56].

Two systematic reviews intended to shed light on overdiagnosis of breast cancer. One of them, performed by Biesheuvel *et al*. concluded that the most reliable overdetection estimates ranged from -4% to 21% and increased with age [22]. The other systematic review, based on published trends in incidence of breast cancer before and after the introduction of mammography screening [53], included five national screening

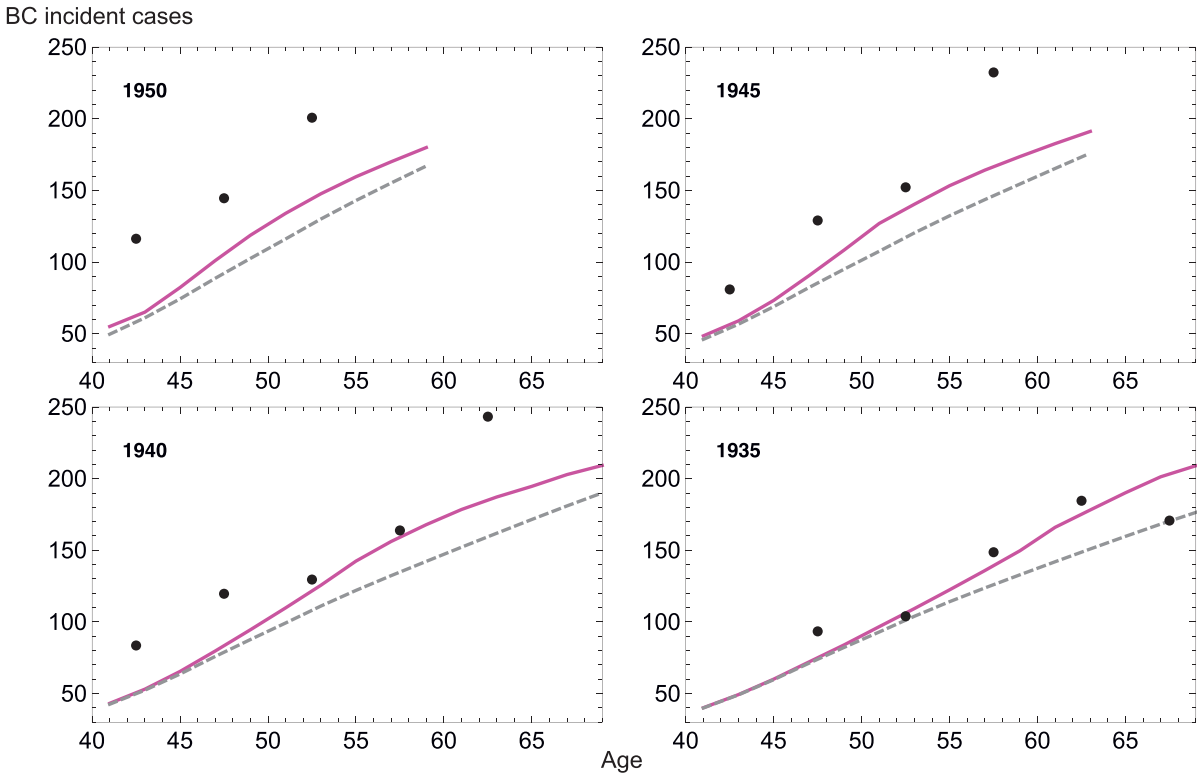

Figure 5 Predicted breast cancer incidence rates per 100,000 women at birth. Each plot shows the results for cohorts born in 1935, 1940, 1945 and 1950: observed (points), background scenario (dashed gray line), and scenario that takes into account the actual dissemination of mammography (purple line).

programs and estimated overdiagnosis in a 35% for invasive cancers.

Two recent observational studies estimated overdiagnosis using population data. Puliti *et al.* [57] evaluated the degree of overdiagnosis of breast cancer 15 years after the introduction of service screening in Florence (Italy). For women aged 60 to 69 years at the start of the screening, the group that had a sufficient follow-up period after the last screening, the authors did not find overdiagnosis. In contrast, Morrell *et al.* [58], in New South Walles (Australia) reported overdiagnosis estimates of 30% and 42% (depending on the method used) for women 50 to 69 years old. Although the study populations and methods used are different, our results are consistent with both Puliti and Morrell studies. Similarly to Puliti, we obtained no overdiagnosis for cohorts born around 1935, which were in their 60 s when mammography began to be widespread in Catalonia. And, consistently to Morrell, we obtained estimates of overdiagnosis higher than 40% for the younger cohorts that had been intensively exposed to mammograms for early detection.

Table 2 Overdiagnosis estimation by year of birth in Catalonia

Cohort	Overdiagnosis (%)	[95% conf. interval]	
1935	0.4	-8.8	12.2
1940	23.3	9.1	43.4
1945	30.6	12.7	57.6
1950	46.6	22.7	85.2

Table 3 Sensitivity analysis for the cohort born in 1945

Screening pattern	Parameter change	Overdiagnosis (%)
Annual (z = 40)	-	26.4
Annual (z = 40)	β = 0.9	25.0
Annual (z = 40)	α = 1	51.1
Annual (z = 40)	α = 5	18.3
Biennial (z = 40)	-	33.9
Mamo dissem 1994 for 40 to 49 years	-	33.8
Mamo dissem 2006 for 60 to 69 years	-	29.3

To test the sensitivity of the model we changed some of the parameters and estimated overdiagnosis for woman born in 1945. The modified parameters were mammography sensitivity (β) and mean sojourn time in pre-clinical state (α). In the first five scenarios, 100% of the population started receiving mammography at age 40 (z = 40). The last two scenarios take into account the actual dissemination of mammography, and use as proportions of repeat mammography behavior the most extreme vañues found in the different health surveys (see Methods).

Zahl *et al*., using a different approach, compared six-year cumulative incidence of invasive breast cancer in a screened and a control group in Norway [51]. All women in the control group were invited to receive a 1-time prevalence screen at the end of the observation period. Since the cumulative incidence among controls never reached that of the screened group (incidence rate ratio = 1.22), the authors suggested that the natural course of some screen-detected invasive breast cancers may be to spontaneously regress. Similarly, Gotzsche *et al*. in the update of the Cochrane systematic review of screening for breast cancer with mammography estimated that screening led to 30% overdiagnosis and overtreatment, a figure consistent with our results [59].

Strengths and weaknesses

This study has several limitations: 1) Incidence data in Catalonia was not available at the population level. The two Catalan population based cancer registries, at the Girona and Tarragona provinces, cover an area of around 20% of the Catalan population. We have assumed that the incidence of breast cancer from these registries, was generalizable to the Catalan incidence. We think that this assumption is acceptable because even the cancer registries are geographically distant within Catalonia, the incidence estimates were close.

Besides, both cancer registries report to the International Agency for Research on Cancer and comply with its quality control procedures. 2) Incidence estimates were available for a 25-year period, therefore some age-specific incidence rates were not available. Although the incidence model estimates were stable and precise, the estimates of overdiagnosis for some cohorts had wide confidence intervals. 3) We did not have information on trends over time of important risk factors like HRT, oral contraceptives, alcohol consumption obesity and sedentarism. We know that the use of HRT has been low in Spain. During the 1990 s, the prevalence of HRT use among Spanish women aged 45 to 64 increased progressively reaching a value of 5.9% in 1998 and declined to 4.2% in 2006 [60,61]. Within a cohort of participants in a population-based breast cancer screening program in the city of Barcelona, the prevalence HRT peaked in 2002 at 11% in 50- to 54-year-olds and at 10.1% in 55- to 59-year-olds, followed by a sudden reversal and a progressive decrease [62]. Prevalence of overweight and obesity in Spain has increased as in the majority of other developed countries. A study of primary care users in the Girona province showed that the proportion of women with obesity ($BMI < 30$ kg/m^2), in the 35 to 44 age group, increased from 6.9% in 1986 to 1989 to 12.9% in 1995 to 1999 [63]. The scarcity of information on risk factors other than fecundity and mammography use led us to include the *year of birth* in the model to represent the remaining cohort effect. 4) Our breast cancer incidence model used grouped data to estimate the association between incidence rates and characteristics of the exposed population at different periods of time. Grouped data analysis may be affected by the ecological fallacy or failure of aggregate level associations to properly reflect individual level associations. We intended to overcome this problem forcing the *completed fertility rate* variable to be inversely associated with breast cancer incidence as reported in the literature. In addition, we included the effect of *year of birth* in the incidence model as linear consistent with an extended increasing trend over time. This assumption provided a more conservative estimate of overdiagnosis than when we fitted a higher degree polynomial function. 5) The estimates of mean sojourn time in a preclinical state that we have used are based on data from the early detection randomized clinical trials [64] which did not take overdiagnosis into account. That would have caused mean sojourn time to appear longer than it was [54]. If mean sojourn time in a preclinical state was smaller than the values we used, our estimates of overdiagnosis would be conservative (see Table 3 where our sensitivity analysis shows the effect of changes in mean sojourn time).

The principal strength of our study is the use of probabilistic models to obtain the expected incidence of breast cancer. Based on the background incidence and the dissemination and patterns of use of mammography in Catalonia we have estimated the increased age-specific incidence due to lead time. Our study does not compare a screened group with a control group, it compares the observed incidence rates with the expected ones assuming that screening detects earlier invasive tumors that would become apparent later during the womens' life.

In comparison with the conventional age-period-cohort (APC) models, our model includes two specific cohort characteristics, the *intensity of mammography use* and the *completed fertility rate*, which have opposite trends during most of the study period. The agreement between the observed and fitted incidence rates for almost all the studied cohorts indicates the relevance of this variables when explaining incidence changes over time and the difficulties in interpreting APC models when they include only one cohort effect that summarizes divergent information.

Conclusions

Our results support the existence of overdiagnosis in breast cancer screening by mammography in Catalonia. Since our overdiagnosis estimates were high in cohorts that have not reached the age of 60, where the impact of competing risks is low, it seems that the limited

malignant potential of some tumors may play an important role in overdiagnosis. As other authors have recommended [20,21], women should be informed about the benefits and harms of screening and research should be oriented towards assessing individual risk and incorporating it to optimize the effectiveness of screening.

Additional material

Additional file 1: Appendix. The file contains further details of the model for dissemination of mammography, equations for the estimation of BC incidence, prevalence, mortality, and overdiagnosis.

Abbreviations

APC: age-period-cohort; BC: breast cancer; BCSP: Catalan Breast Cancer Screening Program; CFR: completed fertility rate; CISNET: Cancer Intervention and Surveillance Modeling Network; DCIS: ductal carcinoma in situ; HRT: hormone replacement therapy; LZ: Lee and Zelen; PM50: proportion of women receiving periodic mammograms at age 50; USA: United States of America.

Acknowledgements

We thank Sandra Lee, Marvin Zelen and Hui Huang for their support in the development of the probabilistic models used. We are also grateful to the anonymous reviewers for their comments and suggestions that have improved the manuscript.

This study has been funded by grants PI06/1649, PI06/90355 and PS09/01340 from the Health Research Fund (Fondo de Investigación Sanitaria) of the Spanish Ministry of Health and by grant 068/27/06 of the Catalan Agency for Health Technology Assessment (Agència d'Avaluació de Tecnologia i Recerca Mèdiques).

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Authors' contributions

MM-A developed the age-cohort model, participated in the statistical analysis of results and interpretation, wrote drafts and obtained authors' feedback and participated in the writing of the manuscript. EV developed the computer programs that estimate the effect of screening under different scenarios, provided statistical analysis and interpretation of results and participated in the writing of the manuscript. RM-G provided the incidence data and participated in writing and revising the manuscript. MR co-developed the project that includes this study, performed statistical analysis and participated in the writing of the manuscript.

Competing interests

The authors declare that they have no competing interests.

Received: 8 April 2010 Revised: 13 July 2010 Accepted: 3 August 2010
Published: 3 August 2010

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doi:10.1186/bcr2620
Cite this article as: Martinez-Alonso *et al.*: Breast cancer incidence and overdiagnosis in Catalonia (Spain). *Breast Cancer Research* 2010 **12**:R58.

APPENDIX

A Estimation of the proportion of women who were having periodic mammograms for early detection at age 50

The following mixed effects model for dissemination of mammography in Catalonia was estimated in a previous work [28]:

$$p = \frac{\phi_1}{1 + exp[(\phi_2 - age)/\phi_3]} \tag{1}$$

were p indicates the proportion of women receiving periodic mammograms, ϕ_1 ($asym$) is the horizontal asymptote as age increases or the proportion at which the curve levels off, ϕ_2 ($xmid$) indicates the age value at which approximately half of the population is receiving periodic mammograms and ϕ_3 ($scal$) indicates the difference in years between the age at which 3/4 of the population are receiving periodic mammograms and the age ϕ_2.

Dissemination curves were estimated for cohorts born in the calendar period 1938 to 1967. We could not estimate dissemination curves for cohorts born before 1938 or after 1967 because data was scarce. The parameters ϕ_1 and ϕ_3 were estimated as fixed effects and the parameter ϕ_2 as random effect.

As shown in Table A1, for cohorts born in the calendar period 1938 to 1967, the proportions of women having periodic mammograms at age 50 were estimated directly from the dissemination equation, setting $age = 50$. For cohorts born before 1938, we used data from the Catalan Health Survey for year 1994 to obtain the proportion of women having periodic mammograms by cohort of birth. For cohorts born after 1967 we used data from the Catalan Health Survey for year 2006. We used these proportions to estimate the random parameter ϕ_2 for each cohort and then we used the equation (1) to estimate the proportion of women having mammograms at age 50.

Table A1.**Number of women interviewed and percent reporting having periodical mammograms. Catalan Health Surveys, calendar years 1994, 2002, and 2006.**

Birth cohort	Parameter $\phi 2$	PM50	Proportion of women having periodic mammograms
1913-1917	96.92	0.0002	0.0335 [a]
1918-1922	88.99	0.0007	0.0563 [a]
1923-1927	80.24	0.0035	0.1067 [a]
1928-1932	70.93	0.0194	0.2094 [a]
1933-1937	64.69	0.0594	0.2497 [a]
1938-1942	56.78	0.2140 [b]	
1943-1947	50.20	0.4750 [b]	
1948-1952	44.76	0.7025 [b]	
1953-1957	41.12	0.8120 [b]	
1958-1962	39.84	0.8406 [b]	
1963-1967	37.33	0.8840 [b]	
1968-1972	41.61	0.7996	0.2523 [c]
1973-1977	39.08	0.8554	0.1764 [c]

[a]Data obtained from the Catalan health survey 1994. [b]Data estimated from the dissemination model. [c]Data obtained from the Catalan health survey 2006.

B Incidence models

Data for the observed incidence model was grouped in 5-year intervals, using the midpoint of the interval as the representative value. Year of birth was estimated as the incidence period midpoint minus the age midpoint. Since breast cancer incidence is very low before age 25 and it is affected by competing risks after 84 years of age, we modeled incidence data from 25 to 84 years of age.

Fractional polinomials were used to model the age and cohort effects on incidence. A fractional polynomial of degree m with powers $p = (p_1, ..., p_m)$ is defined as:

$$FP(m) = \beta_1 X^{p_1} + \beta_2 X^{p_2} + ... + \beta_m X^{p_m}$$

Powers p are taken from a predefined set, for example $\{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$ and power 0 means $log(X)$.

Mammography dissemination was incorporated in the model in the following way. A screening scenario is characterized by a) the proportion of women that receive periodic mammographies at each age and by b) the distribution of the exams' periodicity (annual, biennial and higher periodicity or irregular). We used

proportions from the Catalan survey from 2002 for ages in the 50-59 year interval (annual = 0.61, biennial = 0.33, and irregular = 0.06). The proportion of irregular screening was split into two parts and each one of them was added to the proportions of biennial and non-mammography.

The difference between the proportion of women that use periodic mammography at ages $z+1$ and z is an estimate of the proportion of women that started mammography at age z. We assumed that all women that reported having mammograms at age 40 (initial age) had not received mammograms before. Weighting the estimates obtained for each screening scenario by the pattern of mammography use, we obtained the estimated number of incident cases by age and birth cohort.

C Estimation of the probability of surviving free of BC: $S_\nu(t)$

The probability of surviving free of disease, by cohort of birth ν, is one of the inputs of the mathematical model. $S_\nu(t)$ depends on mortality from causes other than breast cancer (competing risks [37-38]) and BC incidence. To estimate $S_\nu(t)$ we performed the following steps:

1. Obtain the central mortality rate at age u from other causes than breast cancer

$$m^{-bc}(u) = m^{\tau}(u) - m^{bc}(u) \tag{2}$$

   The all-cause and BC central death rates are labeled as m^{τ} and m^{bc}, respectively. The numerators of the central rates are the number of deaths in the age interval. The denominators have been approximated by the number in the population midway through the interval:

2. Assume that the instantaneous force of mortality λ_m^{-bc} is constant over the age interval $[u, u+1)$ and can be approximated by $m^{-bc}(u)$.

3. Obtain the incidence central rate $i(u)$ and assume that it can approximate the instantaneous incidence rate λ_i. Breast cancer incidence was estimated according to the incidence model in Table 1.

4. Obtain the hazard of failure either due to being a BC case or dying from other causes (λ^F). We assume that the two hazards are independent.

$$\lambda^F = \lambda_m^{-bc} + \lambda_i \tag{3}$$

5. Solve the differential equation:

$$S'_\nu(t) = \lambda^F S_\nu(t); \quad S_\nu(0) = 1 \tag{4}$$

D Equations for estimating breast cancer incidence probabilities

D.1 Background scenario

This section refers to the *background* scenario where BC is diagnosed only by routine care with no screening. Data obtained under the background scenario will be compared to data obtained under the screening scenario, therefore some of the notation is common for both situations and follows the work of Lee and Zelen [28].

The age at which the study starts is denoted by z. In the screening scenario z is the age at which the first screening exam is performed and $t_0 = 0$ the time at which the first screening exam is performed or origin time.

There are three chronological times (relative to $t_0 = 0$) that must be taken into account in the formulas. These are: x= the time at which the preclinical state, S_p, is entered, (x can be positive or negative), τ= the time at which the clinical state is entered, and y= the time at death. The corresponding ages are $z + x$, $z + \tau$ and $z + y$ and the sojourn times in S_p and S_c are $(\tau - x)$ and $(y - \tau)$, respectively.

We present the formulas used to estimate BC incidence for a specific cohort ν. Incidence probabilities and mammography sensitivity vary by age and cohort of birth. For simplicity, the index ν that indicates birth cohort is not shown in the notation.

The probability of being incident at the time interval $[t, t + 1)$ can be estimated using the formula:

$$I(t) = \int_t^{t+1} S_\nu(u) i(u) du \tag{5}$$

where $i(u)$ is the age and cohort specific incidence at time u.

D.2 Relationship between BC incidence and transition to the pre-clinical and clinical states S_p and S_c

Under screening we do not observe the time at which a BC will become symptomatic. Therefore, the incidence distribution can not be used in the calculations. Instead, the Lee and Zelen models use the transition probability $S_0 \to S_p$ denoted by $w(t)dt$ and the probability density function of the sojourn time in the preclinical state, $q(t)$ [40].

The following equation shows the equivalence between the estimation of incidence at age $z + k$, $k = 0, 1, 2...$ using the incidence $i(t)$ or the $w(t)$ and $q(t)$ functions.

$$I(z + k) = \int_k^{k+1} S_\nu(z + \tau) i(z + \tau) d\tau \approx \int_k^{k+1} \int_0^z S_\nu(\tau - x) w(\tau - x) q(x) dx d\tau \tag{6}$$

Also, the left side of this equivalence was used for the final estimation of *background* BC diagnosis.

D.3 Screening scenarios

This section presents the formulas used to perform the estimations under a generic screening scenario. A pattern of screening is characterized by age interval and periodicity of exams. Survival distribution functions and stage at diagnosis distribution are pattern specific.

Under a screening scenario, Lee and Zelen distinguish whether BC was detected in a screening exam or if it was diagnosed in the interval between two screening exams.

D.3.1 BC detected at exam r

Lee and Zelen considered n examinations given at chronological times $t_0 < t_1 < ... < t_{n-1}$. The first exam is performed at age z and time $t_0 = 0$. Each successive exam r is performed at time t_{r-1}. For instance:

Exam number (r)	1	2	3	...	r	...	n
Exam time for annual screening, in years (t_{r-1})	0	1	2	...	$r-1$	...	n-1
Exam time for biennial screening, in years (t_{r-1})	0	2	4	...	$2(r-1)$	...	2(n-1)

The probability of detecting a BC in the first exam (t_0) is

$$Det(t_0, z) = \beta(z) \int_0^z S_\nu(z-x) w(z-x) Q(x) dx \tag{7}$$

where

$$Q(t) = \int_t^\infty q(x) dx \tag{8}$$

is the tail probability of the sojourn time in the preclinical state.

The probability of detecting a BC at time t_r, $Det(t_r, z)$ takes into account if the transition to S_p was done before ($Det_{pre}(t_r, z)$) or after ($Det_{post}(t_r, z)$) the age z.

$$Det(t_r, z) = Det_{pre}(t_r, z) + Det_{post}(t_r, z) \tag{9}$$

$$Det_{pre}(t_r, z) = \beta(z + t_r) \left(\prod_{i=0}^{r-1} (1 - \beta(z + t_i) \right) \int_0^z S_\nu(z-x) w(z-x) Q(t_r + x) dx \tag{10}$$

$$Det_{post}(t_r, z) = \beta(z + t_r) \sum_{j=1}^{r} \left(\prod_{i=j}^{i<r} (1 - \beta(z + t_i)) \right) \int_{t_{j-1}}^{t_j} S_\nu(z+x) w(z+x) Q(t_r - x) dx \tag{11}$$

D.3.2 BC diagnosed in the interval (t_{r-1}, t_r)

Women diagnosed in the interval (t_{r-1}, t_r) may have entered the preclinical state S_p:

- before age z
- in the interval (t_{r-1}, t_r)
- in the interval (z, t_{r-1})

The probability of being diagnosed in the interval equals to the sum of these three probabilities. We introduced an additional index, s, that allowed to obtain the estimates yearly when the screening scenario has biennial periodicity or higher . Thus, $s = 0$ refers to the first year of the interval and $s = 1$ to the second year and so on, successively.

Transition to preclinical state before age z:

$$Int_{pre}(r, z, s) = \left(\prod_{i=0}^{r-1} (1 - \beta(z + t_i)) \right) \int_{t_{r-1}+s}^{t_{r-1}+s+1} \int_0^z S_\nu(z - x) w(z - x) q(\tau + x) dx d\tau \tag{12}$$

Transition to preclinical stage in the interval (t_{r-1}, t_r):

$$Int_{post1}(r, z, s) = \int_{t_{r-1}+s}^{t_{r-1}+s+1} \int_{t_{r-1}}^{\tau} S_\nu(z + x) w(z + x) q(\tau - x) dx d\tau \tag{13}$$

Transition to preclinical state in the interval (z, t_{r-1}):

$$Int_{post2}(r, z, s) = \sum_{j=1}^{r} \left(\prod_{i=j}^{i<r} (1 - \beta(z + t_i)) \right) \int_{t_{r-1}+s}^{t_{r-1}+s+1} \int_{t_{j-1}}^{t_j} S_\nu(z + x) w(z + x) q(\tau - x) dx d\tau \tag{14}$$

D.3.3 BC diagnosed in an interval after the last exam, $(t_{n-1} + s, t_{n-1} + s + 1)$, $s = 1, 2, ...$

As in previous sections, the probability equals to the sum of the following:

Transition to the preclinical state before age z:

$$Int_{pre}(n, z, s) = \left(\prod_{i=0}^{n-1} (1 - \beta(z + t_i) \right) \int_{t_{n-1}+s}^{t_{n-1}+s+1} \int_0^z S_\nu(z - x) w(z - x) q(\tau + x) dx d\tau \tag{15}$$

Transition to the preclinical state in the interval $(t_{n-1}, t_{n-1} + s + 1)$:

$$Int_{post1}(n, z, s) = \int_{t_{n-1}+s}^{t_{n-1}+s+1} \int_{t_{n-1}}^{\tau} S_\nu(z + x) w(z + x) q(\tau - x) dx d\tau \tag{16}$$

Transition to the preclinical state in the interval (z, t_{n-1}):

$$Int_{post2}(n,z,s) = \sum_{j=1}^{n} \left(\prod_{i=j}^{i<r} (1-\beta(z+t_i)) \right) \int_{t_{n-1}+s}^{t_{n-1}+s+1} \int_{t_{j-1}}^{t_j} S_\nu(z+x) w(z+x) q(\tau - x) dx d\tau \qquad (17)$$

D.3.4 Probability of being diagnosed

The probability of being diagnosed during a specific calendar year is the sum of the probability of being detected at the exam (if it was performed) and the probability of being diagnosed in the interval between two exams or after the last exam.

E Overdiagnosis

E.1 Example

Figure 1 illustrates the estimation of incident BC cases taking into account the pattern of mammography use reported in the Health Surveys and the assumption of no overdiagnosis, for women born in 1950. The highest age observed for the 1950 cohort was 54 years. Table 1) in the figure shows the number of BC cases for 100,000 women at birth if the age at initial mammography use was z. Column $2 - D^A$ contains the proportion of women that started annual screening at age z, Table 3) has been obtained by multiplying Table 1) by column $2 - D^A$ and contains the number of BC cases from women that use mammography with annual periodicity.

Table 4), column $5 - D^B$ and Table 6) in Figure 1 contain the same information for women that use mammography with biennial periodicity and Table 7), column $8 - D^{bkg}$ and Table 9) for women that do not use screening mammography.

Adding the BC cases of Tables 3), 6) and 9), we obtain an expected cumulative incidence of $CI_e = 1573.9$ in the age interval 40-54, per 100,000 women born in 1950.

To obtain the observed BC cumulative incidence per 100,000 women at birth, first we obtain the 5-year age-specific incidence rates from the data (617.7, 768.3 and 1079.3 per 100,000 women in the age groups 40-44, 45-50 and 50-54 years, respectively). Then we multiply these rates by the probabilities of being alive at each age (0.95, 0.94 and 0.93 for the three age-groups, respectively). Adding up these values we obtain an observed cumulative incidence $CI_o = 2307.6$.

Therefore, the estimated overdiagnosis for cohort 1950 in the age interval 40-54 years was:

$$100 \times \frac{CI_o - CI_e}{CI_e} = 100 \times \frac{2307.6 - 1573.9}{1573.9} = 46.6$$

E.2 Confidence intervals of the overdiagnosis estimates

Bootstrapping was used to obtain 95% confidence intervals of the overdiagnosis estimates. We repeated the following sequence 1,000 times:

1. Draw a random sample with replacement of the residuals $Z_i = \frac{O_i - E_i}{\sqrt{E_i}}$ of the Poisson incidence model, with O_i being the observed number of breast cancer cases and E_i the expected number in an age- and cohort-group i.

2. Use the bootstrapped residuals (Z_i^b) to create a new sample of count data using the expression ($O_i^b = max(0, E_i + Z_i^b\sqrt{E_i})$).

3. Use the values O_i^b to fit a new Poisson model for BC incidence and a corresponding background incidence model. When fitting this model we allowed to vary the form of the fractional polynomial for variable age and maintained the same powers for the other variables.

4. Follow the steps described in the *Overdiagnosis estimation* section to obtain a new overdiagnosis estimate.

The 95% confidence interval limits were obtained using the percentiles 2.5 and 97.5 of the overdiagnosis estimates.

4

OUTCOMES REPORTED FROM SUPPLEMENTATION WITH VITAMIN D (CHOLECALCIFEROL OR ERGOCALCIFEROL) TO ADULT CANCER PATIENTS. A SYSTEMATIC REVIEW

This is a systematic review of all the published clinical research outcomes from cancer patients taking supplements of the inactive forms of vitamin D (D_2 or D_3). A total of 21 original studies have been identified, including observational (retrospective and prospective) and experimental studies, but no randomized controlled trial assessing vitamin D efficacy to improve outcomes in cancer patients. The vitamin D dosages differed markedly. Furthermore, in the 99 studies reporting serum 25-hidroxivitamin D levels, the metabolite used to measure vitamin D status, doses below 2,000 IU/day of either D_2 or D_3 were insufficient to correct vitamin D deficiency.

Outcomes reported from supplemention with vitamin D (cholecalciferol or ergocalciferol) to adult cancer patients. A systematic review

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Abstract

Background

A high prevalence of vitamin D deficiency among cancer patients has been already extensively reported. In the general population, vitamin D deficiency is a recognized risk factor for mortality for all causes despite normal circulating levels of the hormonal form of vitamin D (1,25-dihydroxyvitamin D), the most active endogenous metabolite of vitamin D. Undoubtedly, the safe supplementation with cholecalciferol (vitamin D_3) or ergocalciferol (vitamin D_2) directed exclusively to correct vitamin D deficiency should result in improvements in cancer outcomes.

Aim

To present all existing evidence from clinical studies on outcomes upon supplementing cancer patients with D_2 or D_3.

Methods

This is a systematic review of all published clinical research (only case reports were excluded) supplementing cancer patients with cholecalciferol or ergocalciferol. All studies using already active vitamin D metabolites (calcidiol, calcitriol or analogues) were excluded. The key words used for the literature search included synonyms of vitamin D and cancer in the title, and of supplement and patient either in the title or the abstract, in MEDLINE and SCOPUS. Review articles were not excluded to identify any missed study.

Results

A total of 541 studies were identified till the end of 2014. After reading the abstract, 509 were excluded due to either the use of active vitamin D metabolites or the study of non-adult cancers. The remaining articles included 21 original clinical studies and 10 reviews. Ten (48%) were observational studies, one was a randomized controlled trial, and ten where non-controlled clinical trials. Most participants were either women with breast cancer (10 studies) or men with prostate cancer (4 studies). Even among studies in patients with the same cancer type, the dosage for vitamin D as well as the duration of supplementation differed markedly, thus precluding any meta-analysis on outputs. Doses lower than 1,000 IU/day were not effective to correct serum vitamin D concentrations, whereas higher doses did increase concentration to the normal range.

Conclusion

This review documents the need of well powered randomized controlled trials to obtain evidence based recommendations in support of the impact, or the lack of it, of the correction of vitamin D deficiency on clinical outcomes in cancer patients..

Keywords

cancer; vitamin D; cholecalciferol; ergoferol

Introduction

Background and rationale

Cancer is a leading cause of disease and cause-specific death worldwide. According to data collected until 2012, the World Health Organization (WHO) estimated cancer incidence worldwide in 14.1 million and cancer-specific mortality in 8.2 million in 2012. Lung, female breast, colorectal and stomach cancers accounted for more than 40% of all incident cases diagnosed worldwide in 2012. In men, lung cancer was the most common cancer (16.7% of all new cases). Breast cancer was by far the most common cancer diagnosed in women (25.2% of all new cases). In terms of cancer-specific mortality, more than half of all cancer deaths each year are due to lung, stomach, liver, colorectal and female breast cancers. Given the morbidity and mortality of these malignancies, researchers are exploring new areas for prevention and treatment. Since vitamin D deficiency is a recognized risk factor for mortality for all causes, including cancer, in the general population, the safe and inexpensive correction of vitamin D deficiency through supplementation with cholecalciferol or ergocalciferol could help prevent/attenuate the devastating impact of cancer in the world.

In fact, patients with cancer are highly vitamin D deficient. Data from observational clinical studies and small clinical trials support multiple health benefits from the local actions of the hormonal form of vitamin D upon the correction of serum vitamin D levels. The mechanisms underlying these benefits include the improvement of musculoskeletal function, reinforcement of anti-tumoral action with reduction of the severity of inflammatory responses by immune cells, antiproliferative and anti-angiogenic properties. The benefits of vitamin D supplementation over treatment with active vitamin D metabolites, is the lower impact on hypercalcemia and hyperphosphatemia. The latter is a pro-aging factor that markedly enhances mortality in the general population.

There are two safe and inexpensive approaches for vitamin D supplementation forms, cholecalciferol (D_3) and ergoferol (D_2). Although both metabolites elicit the same potency when administered daily, the half life of 25-hydroxyvitamin D_2 is half of that of vitamin D_3 and consequently, the frequency for non daily supplements should not extend longer than 14 days for D_2, while large doses of cholecalciferol could be administered monthly. The increase in the number of publications on cancer and vitamin D increase led us to examine whether they could provide evidence of dosage, frequency of supplementation and impact on outcome in cancer patients.

Objectives

To identify and summarize all the outcomes published in observational and experimental clinical studies reporting the results obtained from the supplementation of cancer patients with D_2 or/and D_3.

Methods

The present study was designed as a systematic review of all published clinical research, including observational retrospective and prospective studies (in which participants are asked about the amount of vitamin D supplements that they usually take) and phase II

and III clinical trials (in which participants are prescribed with a certain amount of vitamin D).

Only the clinical trials reporting results of supplementation with D_2 or D_3 to adult cancer patients were included in this systematic review. Therefore, children are excluded from the population of study, as well as the studies supplementing with other forms of vitamin D (calcifediol, calcitriol or analogues), due to the differences between cancers occurring in childhood and adulthood, or between the metabolism and actions of the inactive and active forms of vitamin D.

The search strategy implemented in MEDLINE and SCOPUS included an advanced search with the four following key words "vitamin D", "cancer", "supplement", "patient", with synonyms and free suffixes and prefixes. The reviews identified by this search were exhaustively examined to ensure that all relevant references were included in this review.

The final advanced search strategy used was:

Pubmed: (*vitamin* D*[ti] OR *calciferol[ti] OR calcidiol[ti] OR calcife*[ti]) (*cancer*[ti] OR *onco*[ti] OR *carcino*[ti]) (patient*[tiab]) (*treat*[tiab] OR *drug*[tiab] OR *therap*[tiab] OR care[tiab] or supplement*[tiab])

Scopus: (TITLE ("*vitamin* D*" OR "*calciferol" OR "calcidiol" OR "calcife*") AND ABS (patient*) AND TITLE (*cancer* OR *onco* OR *carcino*) AND ABS (*treat* OR *drug* OR *therap* OR care OR supplement*))

Results

A total of 541 references till the end of 2014 were identified. After reading the abstract, the following exclusion criterion was applied: duplicate publications, scientific publications from basic rather than clinical research, clinical trials using vitamin D compounds different from vitamin D_2 and D_3, clinical studies supplementing with vitamin D_2 and D_3, but not reporting results from supplementation, case reports, and childhood cancer. Upon excluding 509 references, 21 original clinical studies (Table 1) were included in this systematic review. The 10 review articles were used to avoid missing any relevant clinical study.

Ten (48%) of the 21 studies were observational, only one was a randomized controlled trial, and the other ten were non-controlled trials that had not been designed with the aim to assess outcomes after supplementation with vitamin D. The participants were mainly women with breast cancer (10 studies) or men with prostate cancer (4 studies). There were 3 studies with miscellanea of cancer types for the participants (Table 2), 2 studies with participants diagnosed of pancreatic carcinoma, 1 study with colorectal cancer patients and 1 with coetaneous T-cell lymphoma. In 6 studies, supplements combined vitamin D and calcium. In 5 studies, the amount of vitamin D (mainly D_3, more frequently investigated than D_2) was from 200 IU to 800 IU/day, and these studies demonstrated the uselessness of such a dose to correct serum vitamin D levels. The most recent publications were highly heterogeneous, some of them suggesting an initial high dose of 100,000 or 150,000 IU to correct vitamin D levels or to keep them in the normal range (>30 ng/mL).

Outcomes were reported upon such heterogeneous supplementation strategies that comparisons are not possible. Furthermore, the most common outcome reported is the proportion of patients that increased serum vitamin D levels above 30 ng/mL, correcting their deficiency. However, even this information was not provided in all the studies. Indeed, some studies only reported the change in the serum vitamin D concentration. In general, trials reported an increase in serum vitamin D till non-deficiency levels (>=20 ng/dL) concentration when using a daily dose of at least 2,000 IU of D_3 (table 3). Five studies reported an improvement in pain associated with vitamin D supplementation. One study reported a significant improvement in disease free survival for those taking vitamin D supplements.

Discussion

The most critical translational contribution of this review is the demonstration of the current need of well powered randomized controlled trials to obtain evidence based recommendations in support of the impact on clinical outcomes (or the lack of it) of appropriate supplementation strategies for the correction of vitamin D deficiency in cancer patients.

The oldest study in this review by Van Veldhuizen et al, in 2000, was the first to suggest that cholecalciferol might have a therapeutic effect in men with advanced prostate cancer. Specifically, they supplemented 16 metastatic androgen-insensitive prostate cancer patients with 2,000 IU of vitamin D3 for 12 weeks to improve bone pain. At baseline, 8 (50%) of these patients had vitamin D levels below 20 ng/mL. After vitamin D supplementation, 4 men (25%) experienced improvement in pain scores and one showed a decrease in PSA from 99.2 to 55.3 ng/mL.

Additional clinical research was conducted with lower and higher vitamin D doses. The review shows that lower doses are not sufficient to raise the serum vitamin D level to the normal range. The review published by Teleni et al at 2013, which included 7 of the studies of our review, suggests that natural sources of vitamin D or vitamin D “daily recommended allowance” are not enough for a cancer patient to reach adequate serum vitamin D concentrations. It was also clear from this review clear from this review the importance of personalizing vitamin D supplementation. The increase in serum 25-hydroxyvitamin D in response to supplementation is not the same for all patients, even within a certain cancer type, with some individuals requiring a much higher dose of cholecalciferol or ergocalciferol to correct vitamin D deficiency.

In Spain and the rest of Europe, the recommended dietary allowance (RDA) is 200 IU/day (5 μg/day) for the general adult population. The European Food Safety Authority includes an exception to avoid bone loss (osteoporosis), where RDA is 800 IU/day from all sources. This review clearly illustrates that the supplementation of cancer patients following the approved recommendations will be useless..

Given recognized benefits of the integrity of the vitamin D endocrine system in improving survival rates for all causes in the general population, and with an impact on key targets for the betterment of the quality of life of cancer patients as those of the relevance of the musculoskeletal function and the control of inflammation and the consequent pain, the manifest lack of randomized controlled trials in cancer is a major gap that could be filled safely and inexpensively by the scientific community to benefit

all cancer patients.

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Study (Author Yr)	Cancer	Spetial characteristics	Design	S & A	Groups
Amir et al 2010	Breast	Bone metastases+Bisphosphonates	T2a	40	D_3 + Ca
Cantor et al 2014	Colon, lung, breast		OR	50	D_3
Cho et al 2013	Pancreas		OR	71	D (observed)
Churilla et al 2012	Cancers*	Consultation to radiation oncology	Ta	118	D_3
Crew et al 2009	Breast	adjuvant chemotherapy	Tb	103	D_3
Davison et al 2012	Prostate	Androgen deprivation therapy	OP	51	Education on D_3 + Ca
Fakih et al 2012	Colorectal		Ta	50	D_3
Khan et al 2010	Breast	Adjuvant letrozole	Tb	51	D_3 + Ca
Klapdor et al 2012	Pancreas	Exocrine pancreatic insuficiency	Tb	51	D_3 , individualized
Marshall et al 2012	Prostate	T1c or T2a and Gleason=6	Tb	48	D_3
Nogues et al 2010	Breast	Early with aromatase inhibitors	Tb	232	D_3 + Ca
Peppone et al 2011	Breast		OR	166	D_2 or D_3
Rastelli et al 2011	Breast	Aromatase inhibitors	T2a	60	D_3 + (Ca & D_2 /placebo)
Simmons et al 2009	Breast	Bone Metastases+Bisphosphonates	Tb	46	D_3 in cases
Talpur et al 2014	Lymphoma	Cutaneous T-Cell lymphoma	OP	156	D_2 or D_3
Van Veldhuizen et al 2000	Prostate	Metastasic	T2b	16	D_3
Vashi et al 2010	Cancers**		OR	799	D_3
Waltman et al 2009	Breast	Aromatase inhibitor	OP	29	D_3 + Ca
Wang-Gillam et al 2008	Breast	Bisphosphonates	OR	120	D_3
Woo et al 2005	Prostate	Survivors	OP	15	D_3
Zeichner et al 2014	Breast	Her2+ no mestastasic	OR	134	D (observed)

Note: OR: Observational and retrospective study; OP: Observational and prospective study; Tb: Clinical trial designed with a different primary outcome; Ta: Clinical trial with vitamin D correction as aim. S & A stands for supplemented and analyzed numer of patients.
* 22% Breast; 21% Prostate; 14% Thyroid; 8% Lung; 5% Colorectal; 31% others. **22.7% Breast; 14.9% lung, 9.7 pancreas, 9.3 colorectal, 8.4% prostate, 34.9% others.

Table 1. Description of results for cancer patients supplemented with vitamina D (chole- or ergocalciferol)

	Women %	Age median	AJCC stage	Compliance	Vit. D duration
Amir et al 2010	100%	55	Bone metastases	95.0%	4 mhs
Cantor et al 2014	NA	NA	NA	100.0%	2 wks
Cho et al 2013	46%	90% >=50 y	I y II: 36%, III y IV: 64%	NA(observational)	NA
Churilla et al 2012	50%	64	4% in situ; 26% in I; 32% in II; 18% in III; 16% in IV; 5% other	NA	NA (median 87 days between vitamin D determinations)
Crew et al 2009	100%	43	34% in I; 60% in II and 6% in III	82.5%	1 yr
Davison et al 2012	0%	mean(SD) 71.7(9.1)	Non-metastatic	83.6%	1 yr
Fakih et al 2012	44%	60	6%: II; 40%: III; 54%: IV	100.0%	6 mhs
Khan et al 2010	100%	56	61.7%: I; 8.3%: II; 3.3%: III; 1.7%: IV; 25%NA	85.0%	16 wks
Klapdor et al 2012	100%	NA	NA	72.8% supplemented	Varying
Marshall et al 2012	0%	65	T1c or T2a	92.3%	1 yr
Nogues et al 2010	100%	mean(SD) 63.2(8.7)	Early stage	95.7%	3 mhs
Peppone et al 2011	100%	NA	0-III stage	56.3%	8-16 wks
Rastelli et al 2011	100%	NA	I-IIIB stage	78.3%	6 mhs
Simmons et al 2009	100%	NA	NA	NA	NA
Talpur et al 2014	NA	NA	NA	NA	NA
Van Veldhuizen et al 2000	0%	mean 67.5	IV	100.0%	12 wks after 4 wks placebo
Vashi et al 2010	63%	mean 55.4	0: 1.3%, I: 12.0%, II: 20.5%, III: 23.4%, IV: 34.4%, indeterminate: 8.4%	48.4% for 25(OH)D<=32ng/mL	median 10.9 wks (from 4 to 97.1 wks)
Waltman et al 2009	100%	NA	0: 3.4%, I: 51.7%, II: 44.9%	92.5% adherence	24 mhs
Wang-Gillam et al 2008	NA	NA	NA	NA	NA
Woo et al 2005	0%	Not reported	T1C in 6.7%; T2A in 26.7%; T2B in 20%; T2C in 33.3%; T3 in 13.3%	NA	8 mhs in median (from 4 to 21)
Zeichner et al 2014	100%	mean(SD) 53.0(12.1)	100% non-metastasic	NA	Not reported (during adjuvant therapy)

Table 2. Participants & follow-up of the studies

Study (Author Yr)	Vit.D Supplement	Results
Amir et al 2010	10,000 IU D3 + 1000 mg Ca/day for 4 mhs	No changes in bone resorption nor pain values; Decrease in number of sites of pain; Increase in serum Ca; Decrease in PTH; 5% hypercalcemia; 25(OH)D increased 69.5 : 162 nmol/L in 4 mhs
Cantor et al 2014	High dose of D3 on day 1 + 4,000 IU/day during 2 wks; D3 was 300,000 IU or 150,000 IU on day 1 depending on 25(OH)D <15 (n=18) or [15,30) ng/mL (n=32)	No patient <20ng/mL after supplementation; 11% <30ng/mL; no toxicity
Cho et al 2013	50,000 IU vit. D /wk x 10-12 wks	55%<30ng/mL within the supplemented Group
Churilla et al 2012	50,000 IU D3/wk x 8wk for <30.0 ng/mL + 1,000 IU/day	76(64.4%) with available posttreatment data. They changed mean serum 25(OH)D: 20->35 ng/mL
Crew et al 2009	400IU D3+1000mg Ca/day	60%<20; 29% in [20,30); 11% >=30.
Davison et al 2012	1500 mg Ca + 20-25mcg D3 (800 IU-1,000IU)/day	Inadequate vit. D intake (<20mcg) increased from 70.6 to 76.5%. Inadequate Ca intake (<1,200 mcg) decreased from 56.9% to 43.1%.
Fakih et al 2012	2000 IU/day for 6 mhs	Mean 25(OH)D increased from a mean of 17.5ng/mL to 31.6ng/mL at 3 mhs and 33.8ng/mL at 6 mhs. At 3 mhs, 92% of chemotherapy free patients increased >=10ng/mL (vs. 39% with chemot.)
Khan et al 2010	1200 mg Ca+600IU D3 for 4 wks; If >40ng/mL, go on and if not, change to 50,000 IU D3 for 12 wks (13&42)	100% with >40ng/mL; no toxicity; In n=42, higher frequency with no disability from joint paint, vasomotor and physical QoL (MEN-QOL) in women with >66ng/mL (median). No significant BFI
Klapdor et al 2012	From 1000IU/day to 20,000IU/day depending on the underlying disease and the mal-digestion/assimilation	0% deficiency;15.7% in [20,30) in short-term supplementation; 4.2% in [20,30) in long-term supplementation with doses from 7,000 to 140,000 IU/wk to maintain in 30-59 ng/mL
Marshall et al 2012	4000 IU/day for 1 yr	Change in the num. of + cores (biopsy): 55% decreased, 34% increased); No insufficient; No tox.
Nogues et al 2010	1000 mg Ca+800IU D3/day all; If body mineral densidy<-2 + Bisphosphonates; if 25(OH)D deficiency + 16,000IU/2wks for 3 mhs	23.48% < 30ng/mL post supplementation
Peppone et al 2011	None (n=58) ,1000 IU/day (n=104) or >=50,000IU/wk (n=62) for 8-16 wks	Significant increase in 25(OH)D for >=50,000IU/wk but not for 1,000 IU/day referred to no-suppl.
Rastelli et al 2011	1000mg Ca+400IUD3 for all. Randomized to placebo or 50,000IU/wk of D2 for 8wks if 25(OH)D in [20,30) or16wks if in [10,20) plus 50,000 IU/mth for 6 mhs	11.5%>=30ng/mL in placebo group; 42.9% in D2 group. Pain scores were better for the D2 group after 2 mhs of treatment. Overalll, pain scores were better for the D2 group with <20ng/mL
Simmons et al 2009	400 IU/day	18%<=40nmol/L; 62%(<=70nmol/L) after treatment
Talpur et al 2014	D2 50,000 units biweekly or D3 1000 units/day orally	55(35%) corrected (>30 serum vit D)
Van Veldhuizen et al 2000	2,000IU/day x 12 wks	25% improved pain & 37.5% improved strength
Vashi et al 2010	8,000IU/day of Vit.D if <=32ng/mL	Patients with prostate and lung cancer had the highest percentage of responders (25(OH)D> 32ng/mL in 70% and 69.2%) while those with colorectal and pancreas had the lowest (46.7%)
Waltman et al 2009	1200 mg Ca+ 400 IU D3/day for 24 mhs	6.9%<20ng/mL;79.3% in [20,30). Vit D levels are related with pain
Wang-Gillam et al 2008	<400 IU/day ;400-600 IU/day;>600 IU/day in n=32,41,8	In 81: 27.2%<20ng/mL;30.9% in [20-30) ng/mL
Woo et al 2005	2000 IU/day of D3	Only results on PSA levels are reported.
Zeichner et al 2014	60% <=1400IU/day	8.2%<20ng/mL after supplementation (40.3% missing). In VitD, better DFS (HR=0.36)

Table 3. Supplementation protocols and reported outcomes description

5

VITAMIN D DEFICIENCY AND ITS ASSOCIATION WITH FATIGUE AND QUALITY OF LIFE IN ADVANCED CANCER PATIENTS UNDER PALLIATIVE CARE. A CROSS-SECTIONAL STUDY

This paper is currently under peer-review in *Palliative Medicine*.

This cross-sectional study presents a novel and significant association between vitamin D deficiency and patient's perceived fatigue, physical functioning and quality of life. Fatigue was, in average, the symptom with the highest adverse impact on daily life performance. Currently, there is no effective therapeutic approach for decreasing fatigue. Our findings suggest that a safe intervention to increase serum levels of vitamin D may result in a significant improvement in quality of life in advanced cancer patients.

Vitamin D deficiency and its association with fatigue and quality of life in advanced cancer patients under palliative care. A cross-sectional study

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Abstract

Background

A normal vitamin D status is required for bones and muscles to maintain their structure and function, but it also contributes to the structural and functional integrity of other multiple physiologic systems in the body.

Aim

To assess the relationship of Vitamin D deficiency with health-related quality of life issues, fatigue and physical functioning in advanced cancer patients.

Design

This is a cross-sectional study.

Patients/Settings

Adults under palliative care, having a locally advanced or metastatic or inoperable solid cancer.

Results

Among 30 patients in palliative care with advanced solid cancer, 90% were vitamin D deficient. Serum Vitamin D concentration was positively correlated with patient-reported absence of fatigue (s=0.49), and physical and functional well-being (s=0.44 and =0.41, respectively, $p<0.01$). Fatigue was the symptom with the highest median impact on their lives and was the only one associated with serum vitamin D levels (p=0.031), with lower fatigue in patients with vitamin D concentrations in the third tertile. There was no evidence of a direct association between health-related quality of life and vitamin D status.

Conclusion

The 90% frequency of advanced cancer patients with vitamin D deficiency, together with the positive correlation of vitamin D status with the absence of fatigue and improved physical and functional well-being, points to vitamin D supplementation as a potential effective intervention to enhance the patient's quality of life.

Keywords

advanced cancer; palliative care; vitamin D; quality of life; fatigue

Introduction

Background and rationale

Vitamin D is actually not a vitamin but a pro-hormone, as it is produced endogenously when ultraviolet rays from the sun light interact with the skin. It can also be obtained from fortified foods and a few unfortified foods but mostly, through supplementation. Vitamin D is a fat-soluble inactive compound and becomes biologically active through two hydroxylations, the first one occurring in the liver (converting vitamin D to 25hydroxyvitamin D, also called 25(OH)D or calcidiol) and the second one in the kidney where 25(OH)D is transformed into 1,25-dihydroxyvitamin D, also called 1,25(OH)2D or calcitriol, the hormonal form of vitamin D and, consequently, the most active endogenous vitamin D metabolite [1].

Serum 1,25(OH)2D has a short half-life of 7-8 hours. Its synthesis is tightly regulated by serum parathyroid hormone, fibroblast growth factor 23 (FGF23), calcium and phosphate concentrations, and its circulating level does not typically decrease until vitamin D deficiency is severe [2,6], resulting in a bad indicator of the status of vitamin D [5]. In contrast, serum 25(OH)D has a relatively long circulating half-life of 15-18 days [5]. Because vitamin D conversion to 25(OH)D is loosely regulated, it better reflects the circulating level of vitamin D that a person obtains through the aforementioned sources [1]. Due to the difficulties in measuring vitamin D levels directly, measurements of 25(OH)D are used to estimate the status of vitamin D. The optimal serum 25(OH)D concentration is controversial but, for skeletal health, experts agree that levels lower than 20 ng/mL (it is, 50 nmol/L) are suboptimal.

Normal bone mineralization and growth are both promoted by a normal vitamin D status, which protects children from developing hypocalcemic tetany and rickets, and adults from osteomalacia and osteoporosis [1,2]. Normal vitamin D is also required to maintain the integrity of muscle structure and function [7]. Furthermore, Indeed, vitamin D is involved in the modulation of cell growth (proliferation, differentiation, and apoptosis) in multiple cell types, neuromuscular and immunological functions, and in reducing inflammation and inflammation-driven multiorgan damage [1,3,4]. Despite epidemiologic data suggesting that vitamin D may have a protective effect against colon cancer, the evidence is not as strong for its protective effects against prostate, breast, and cancers at other sites [1]. Most of these non-classical adverse effects of vitamin D deficiency are mediated by the defective local conversion of circulating 25(OH)D to 1,25(OH)2D by bone, muscle, and immune cells, and not by low circulating 1,25(OH)2D, as serum 1,25(OH)2D remains within the normal range until 25(OH)D falls below 4 ng/ml.

Based upon: 1) the significant fatigue, physical and functional impairment in patients with advanced cancer, 2) the very limited therapeutic measures currently available to reduce them, and 3) the benefits of a normal vitamin D status on the functional integrity of multiple physiologic systems in the body, we hypothesized that a significant proportion of patients with advanced cancer in palliative care is vitamin D deficient, ie 25(OH)D <20 ng/ml, and that there is an association between serum vitamin D levels and both the patient's self-assessment of quality of life, and the patient's capacity to perform daily living activities.

Objectives

The objectives are to estimate the proportion of patients with advanced cancer in palliative care who present with serum vitamin D deficiency and to establish the relationship between serum vitamin D levels and the patient-perceived quality of life, as well as their physical condition, functional capacity and fatigue.

Methods

Study design and setting

The present study was designed as a cross-sectional study in palliative care cancer patients.

Participants were in- and out-patients who satisfied the inclusion and exclusion criteria and were examined at the Hospital Universitari Arnau de Vilanova, in Lleida, Spain, from March 2013 to August 2014.

Participants

Eligible patients were adults under palliative care because of a locally advanced or metastatic or inoperable solid cancer, upon signing an informed consent. Since this study evaluates patient-perceived outcomes, patients having a Karnofsky < 30%, a cognitive deterioration (more than 5 mistakes in Pfeiffer test), or suffering from significant pain, dyspnoea, nausea or vomiting (more than 6 out of 10 in the corresponding Numerical Rating Scale 0:10) were excluded. Additional exclusion criteria included pregnant or breast-feeding females, patients undergoing severe liver or renal (GFR < 60) failure, or those who had received chemo or radiation therapy within the last 3 weeks prior to inclusion, or with the possibility of initiating a new cycle of chemo or radiation therapy within a period of 6 weeks after their inclusion.

Variables

Data collection was performed prospectively after approval of the study protocol by the hospital's ethics committee.

Vitamin D

Quantification of serum levels of 25-hydroxyvitamin D (25(OH)D) were measured in ng/mL using the Chemoluminescence-Immuno assay on the Liaison XL Analyzer (DiaSorinOR) in the Central Laboratory at the HUAV.

Primary and secondary end-points

Health-related quality of life (HRQoL) was considered the primary outcome and was assessed using the global health status/quality of life item from EORTC QLQ-C15-PAL, a questionnaire developed for palliative care cancer patients. Scores range from 0 (poor) to 100 (excellent).

Cancer-related fatigue was considered a secondary outcome and was assessed using the fatigue subscale of the FACT questionnaire. This is a widely used 13-item fatigue subscale where each item is a five-point Likert self-reported scale ranging from 0 =”not at all” to 4 = ”very much so”. The total score varies from 0 = ”worst condition” to 52 = ”best condition”.

Other patient-reported secondary outcomes included rates on: 1) the impact of fatigue, pain, dyspnoea, constipation, appetite loss, nausea/vomiting and insomnia, 2) physical and emotional functioning, 3) physical and functional well-being, and 4) functional capacity in the activities of daily living. The rates on the impact of symptoms were assessed using the questionnaire EORTC QLQ-C15-PAL, with scores ranging from 0 (none) to 100 (the highest) for negative impact on daily life. This questionnaire also includes the assessment of physical and emotional functions, both expressed as scores from 0 (poor) to 100 (excellent). The physical and functional well-being were assessed using the FACT questionnaire with scores varying from 0 = ”worst condition” to 28 = ”best condition”. The addition of these two scores to the FACT estimation of fatigue is known as ”Trial Outcome Index”. Finally, the patient-reported functional capacity in the activities of daily living was assessed using the Barthel’s Scale, an ordinal scale that measures performance from 0 (completely dependent) to 100 (independent).

Clinician-reported patient’s performance status was assessed with the Karnofsky and the Palliative Performance Scales (PPS). Both provide a score from 100 to 0, where 100 indicates no evidence of disease (normal performance) and 0 indicates death.

Covariates

Patients’ socio-demographic characteristics (age, gender and educational level), anthropometric characteristics (height, weight, body mass index, and tricipital skinfold thickness), primary tumour (coded according to the ICD 10), tumour stage, and standard serum chemistries (25(OH)D, hemoglobin, leukocytes, lymphocytes, platelets, triglycerides, total cholesterol, total proteins, albumin, liver transaminases ALT and AST, C-reactive protein, phosphorus, creatinine, calcium), and urinary chemistries (creatinine, calcium and microalbumin).

Sample size

Sample size was established to estimate a correlation coefficient between 25(OH) D serum levels and self-perceived quality of life equal to or greater than 0.5, with 95% confidence (bilateral) and 80% statistical power. Based on these considerations, a minimum of 30 patients is required.

Statistical methods

A descriptive analysis of the study sample was performed using the usual summary measures for qualitative and quantitative variables. The proportion of vitamin D deficiency, with 95% confidence interval was estimated with the exact Binomial distribution. The relationship of 25(OH)D serum levels with the quantitative end-points was assessed graphically (scatterplots) and by estimating the Spearman's rank correlation coefficients. Associations between quantitative end-points and 25(OH)D were also checked by grouping patients according to 25(OH)D tertiles. These associations were assessed graphically (boxplots) and statistically by using the Kruskal Wallis test. A significance level of 5% and the statistical software R [11] were used.

Results

Participants

Table 1. Description of the patients (N=30)

	Summary measure
Men	23 (76.7%)
Age (years)	60.5 [55.5;71.0]
Educational level (n=27):	
Illiterate	2 (6.7%)
Primary-High school	22 (83.3%)
College	3 (10.0%)
BMI (kg/m^2) (n=27)	24.3 [21.1;27.7]
Tricipital skinfold thickness (cm) (n=28)	1.5 [1.0; 2.0]
Malignant neoplasma of:	
Hypopharynx (C13)	2 (6.7%)
Esophagus (C15)	2 (6.7%)
Colon (C18)	4 (13.3%)
Rectum (C20)	1 (3.3%)
Anus / anal canal (C21)	1 (3.3%)
Gallbladder (C23)	1 (3.3%)
Pancreas (C25)	2 (6.7%)
ill-defined digestive organs (C26)	1 (3.3%)
Larynx (C32)	1 (3.3%)
Bronchus and lung (C34)	5 (16.7%)
Breast (C50)	1 (3.3%)
Corpus uteri (C54)	1 (3.3%)
Uterus (C55)	1 (3.3%)
Prostate (C61)	3 (10.0%)
Kidney(C64)	2 (6.7%)
Brain (C71)	2 (6.7%)
Tumour stage:	
3	2 (6.5%)
4	28 (93.5%)

Note: Qualitative characteristics are described as absolute number and relative frequency (%). Quantitative characteristics are described as median [interquartile interval]

The participants' characteristics are shown in Table 1. A total of 30 patients was consecutively included after checking eligibility criteria. The study participants were primarily men (76.7%), had low educational levels (60.1%), were in average 63.3 (SD=10.97) years old and had an average body mass index of 24.4 (SD=5.07). The distribution of primary tumours was heterogeneous, being the most frequent in the digestive system (14, 46.7%), followed by those from the respiratory (6, 20.0%), reproductive (5, 16.7%), urinary (2, 6.7%), and nervous (2, 6.7%) systems. Patient's disease stage was, mainly, metastasic. Regarding blood test results, patients had clinically significant low levels of serum total protein, hemoglogin and percentage of lymphocytes and high levels of C-reactive protein, with medians and interquartile intervals of 5.6 [5.2;6.2] g/dL, 10.4 [9.3, 11.7] mg/dL, 11.0% [6.1%, 13.4%] and 22.9 [7.05;63.8], respectively (Table 2).

Table 2. Chemistries

	Patients' summary measures	Hospital reference values	Patients within normal range
S.Creatinine (mg/dL)	0.72 [0.57; 0.83]	0.5-1.4	80%
S.Calcium (mg/dL)	8.44 [7.94; 8.83]	8.6-10.2	40%
S.Phosphorus (mg/dL)	2.97 [2.37; 3.44]	2.7-4.5	60%
S.Total cholesterol (mg/dL)	160.5 [131.3;184.8]	150-220	50%
S.Triglycerides (mg/dL)	144.0 [94.3;203.0]	50-200	73%
S.Total proteins (g/dL)	5.61 [5.19; 6.19]	6.6-8.7	7%
S.Albumin (g/dL)	3.10 [2.83; 3.38]	3.4-5.2	27%
S.Aspartate Transaminase (U/L)	19.0 [15.3; 26.5]	5-38	87%
S.Alanine Transaminase (U/L)	18.5 [14.0; 26.5]	5-40	87%
S.C-reactive proteína (mg/L)	22.9 [7.1; 63.8]	0-6	20%
S.25(OH)D (ng/mL)	8.5 [6.7; 12.6]	30-100	3%
U.Creatinine (mg/dL) (n=19)	47.8 [32.5; 84.6]	39-259	63%
U.Calcium (mg/dL) (n=19)	6.60 [3.10; 9.65]	5.2-35.7	63%
U.Microalbumin (mg/L) (n=18)	5.77 [1.9; 22.3]	0.01-20	61%
S.Leukocytes (x10x9/L)	10.2 [7.9; 13.2]	4.8-10.8	47%
S.Hemoglobin (gr/dL)	10.4 [9.3; 11.7]	13.0-18.0	17%
S.Platelets (x10x9/L)	275.0 [232.3;346.0]	140-450	93%
S.Lymphocytes (%)	11.0 [6.1; 13.4]	17-51	17%
S.Lymphocytes (x10x9/L)	1.09 [0.78; 1.46]	0.9-5.2	60%

Note: Summary measures represent median [interquartile interval]. References values are the normal range used at the hospital.

Vitamin D distribution

The vast majority of patients showed vitamin D deficiency, and the three subjects with levels over 20 ng/dL stand out as outliers, with a clearly asymmetric distribution. The proportion of patients with vitamin D deficiency was 90%, with an estimated 95% confidence interval of IC95%[73%, 98%]. The two tertiles were 7.6 and 10.5 ng/dL. Based on these values, the sample was partitioned into patients with values lower than 8 (n=12), from 8 to values lower than 11 (n=9), and patients with concentrations of 11 or higher (n=9).

Clinician-reported performance status

Both performance status scales scores, KPS and PPS, showed a median of 60.0, and interquartile intervals of [50.0;60.0] and [52.5;60.0], respectively. Thus, an average participant required occasional assistance but was able to care for most of their personal needs (Table 3).

Table 3. Physical performance and patient-reported outcomes

	Patients' summary measures	Score range, best score
KPS (Karnofsky performance scale), from 0 to 100, +	60.0 [50.0;60.0]	[0;100], 100
PPS (Palliative performance scale), from 0 to 100, +	60.0 [52.5;60.0]	[0;100], 100
Barthel, from 0 to 100, +	85.0 [61.3;98.8]	[0;100], 100
PWB (Physical well-being), +	15.0 [11.5;20.0]	[0; 28], 28
FWB (Functional well-being), +	10.0 [6.00;12.0]	[0; 28], 28
FS (FACIT Fatigue score), +	20.3 [14.0;34.8]	[0; 52], 52
TOI (PWB+FWB+FS), +	45.0 [32.3;68.3]	[0;108], 108
Pain impact, -	41.7 [4.17;95.8]	[0;100], 0
Dyspnoea impact, -	33.3 [0.00;66.7]	[0;100], 0
Insomnia impact, -	33.3 [0.00;66.7]	[0;100], 0
Appetite loss impact, -	33.3 [0.00;91.7]	[0;100], 0
Constipation impact, -	33.3 [8.33;100]	[0;100], 0
Fatigue impact, -	66.7 [47.2;100]	[0;100], 0
Nausea/Vomiting, -	0.00 [0.00;16.7]	[0;100], 0
Physical functioning, +	33.3 [13.3;60.0]	[0;100], 100
Emotional functioning, +	50.0 [41.7;79.2]	[0;100], 100
Overall quality of life, +	50.0 [33.3;62.5]	[0;100], 100

Note: Values represent median [interquartile interval]. Symbols + and – indicate that high scores mean better or worse health status, respectively, in reference to the patient measured outcome.

Patient-reported outcomes

Patient-reported outcomes are summarized in Table 3. Overall quality of life (QL) showed a median of 50.0, with quartiles 33.3 and 62.5. Emotional functioning (EF) showed the same median score but more variability. In contrast, physical functioning (PF) showed much lower scores.
The median performance of daily living activities according to Barthel scale (BS) was estimated to be 85 out of 100, with first and third quartiles 61.3 and 98.8, denoting autonomy.
The median of patient's fatigue (FS) assessment (using FACT-F subscale) was 20.3 out of 52 (52 being equivalent to absence of fatigue). Physical and functional well-being (PWB and FWB respectively) were scored with a median of 15.0 and 10.0, respectively, out of 28 (28 being the value denoting the best condition).

The patient's impact of symptoms score ranged from 0 (none) to 100 (the highest impact). Among all the symptoms, fatigue demonstrated the highest impact, with a median 41.7, followed by pain, dyspnoea, sleep, appetite loss and constipation, with a median of 33.3. By contrast, more than 50% of patients reported no impact of nausea/vomiting.

Vitamin D relationships

Table 4. Association between serum 25(OH)D concentrations and patient's age, body mass index, tricipital skin fold and chemistries.

	Spearman rho	25(OH)D <8	25(OH)D [8.0,11.0)	25(OH)D >=11	K-W
Age (years)	-0.13 (0.480)	70.0 [58.5;76.8]	59.0 [55.0;62.0]	58.0 [54.0;71.0]	0.180
BMI (kg/m^2)	-0.14 (0.490)	24.3 [20.9;26.4]	26.0 [24.2;29.3]	23.6 [20.4;26.5]	0.596
Tricipital skinfold thickness (cm)	0.25 (0.207)	1.30 [1.03;1.58]	1.10 [1.00;2.00]	1.90 [1.00;2.10]	0.471
S.Creatinine (mg/dL)	-0.07 (0.718)	0.78 [0.58;1.01]	0.66 [0.50;0.77]	0.72 [0.59;0.78]	0.657
S.Calcium (mg/dL)	0.40 (0.031)	8.04 [7.60;8.58]	8.51 [8.40;8.83]	8.71 [8.33;8.84]	0.127
S.Phosphorus (mg/dL)	0.41 (0.023)	2.52 [2.13;3.00]	3.03 [2.59;3.31]	3.35 [3.22;3.94]	0.071
S.Total colesterol (mg/dL)	-0.13 (0.481)	160.5 [145.3;180.8]	175.0 [142.0;185.0]	130.0[116.0;188.0]	0.452
S.Triglycerides (mg/dL)	-0.43 (0.019)	162.5[126.0;224.5]	180.0[122.0;208.0]	93.0 [83.0;113.0]	0.040
S.Total proteins (g/dL)	0.23 (0.212)	5.57 [4.99;6.23]	5.68 [5.52;6.10]	5.50 [5.40;6.53]	0.674
S.Albumin (g/dL)	-0.02 (0.911)	3.15 [2.90;3.43]	2.90 [2.80;3.10]	3.20 [2.80;3.30]	0.647
S.Aspartate Transaminase (U/L)	-0.24 (0.210)	21.0 [14.8;25.8]	20.0 [18.0;37.0]	16.0 [15.0;17.0]	0.100
S.Alanine Transaminase (U/L)	-0.01 (0.957)	17.5 [14.0;20.5]	27.0 [20.0;64.0]	14.0 [12.0;25.0]	0.013
S.C-reactive proteína (mg/L)	0.05 (0.782)	22.9 [6.35;30.8]	23.0 [9.30;68.2]	14.7 [9.00;134.0]	0.963
U.Creatinine (mg/dL)	0.02 (0.951)	61.4 [32.5;74.8]	62.5 [42.9;87.8]	45.9 [22.4;69.9]	0.579
U.Calcium (mg/dL)	0.25 (0.297)	1.80 [1.15;7.95]	6.60 [4.94;10.7]	8.00 [5.70;9.65]	0.239
U.Microalbumin (mg/L)	-0.33 (0.188)	22.8 [15.3;39.4]	11.3 [1.89;42.0]	2.32 [1.88;4.00]	0.118
S.Leukocytes (x10x9/L)	-0.17 (0.361)	11.31 [8.11;15.8]	9.86 [8.78;11.4]	9.28 [4.55;13.2]	0.619
S.Hemoglobin (gr/dL)	0.20 (0.298)	10.55 [9.60;11.3]	9.70 [8.50;11.6]	11.1 [10.2;13.7]	0.251
S.Platelets (x10x9/L)	-0.34 (0.069)	288.0 [248.0;325.0]	350.0 [230.0;381.0]	233.0[180.0;279.0]	0.256
S.Lymphocytes (%)	-0.08 (0.677)	9.95 [6.55;13.43]	11.8 [8.10;12.20]	11.0 [4.10;13.70]	0.792
S.Lymphocytes (x10x9/L)	-0.15 (0.433)	1.25 [0.89;1.43]	0.95 [0.78;1.45]	0.87 [0.44;1.46]	0.829

Note: S and U indicates serum and urinary chemistries. Spearman's rank correlation coefficient with serum 25(OH)D concentrations and its p-value in brackets are shown in the second column. Columns from third to fifth represent the median, [first; third quartiles] for each of the 25(OH)D tertiles. The last column shows the Kruskal-Wallis test p-value for the differences between the three groups for each of the analyzed parameters.

The results of blood and urine tests showed some statistically significant relationships with serum 25(OH)D concentration (Table 4). Specifically, serum phosphorus and calcium showed positive and statistically significant Spearman's rank correlations of 0.41 and 0.40 respectively whereas triglycerides showed a negative and statistically significant Spearman's rank correlation of -0.43. All these correlations were confirmed when partitioning participants according to the tertiles of serum vitamin D levels. In addition, a significant association was found for serum Alanine Transaminase concentration, with significantly higher values for the second tertile of 25(OH)D.

Clinician-reported performance status showed a positive Spearman's rank correlation with serum 25(OH)D concentration according to both performance scales (0.37 for KPS and 0.40 for PPS). Both correlations were confirmed when partitioning participants according to the tertiles of serum vitamin D levels (Table 5).

Table 5. Association between serum 25(OH)D concentrations and either performance status or patient's reported outcomes.

Table 5	Spearman rho	25(OH)D <8	25(OH)D [8.0,11.0)	25(OH)D >=11	K-W
Barthel,+	0.34 (0.069)	65.0 [53.8;85.0]	90.0 [85.0;95.0]	100.0 [70.0;100]	0.083
KPS (K. performance scale),+	0.37 (0.043)	50.0 [50.0;60.0]	60.0 [50.0;60.0]	60.0 [60.0;70.0]	0.092
PPS (P. performance scale),+	0.40 (0.031)	55.0 [50.0;60.0]	60.0 [60.0;60.0]	70.0 [60.0;80.0]	0.031
PWB (Physical well-being),+	0.44 (0.014)	14.5 [10.5;15.3]	13.0 [10.0;14.0]	22.0 [20.0;24.0]	<.001
FWB (Functional well-being),+	0.41 (0.026)	6.50 [4.00;10.5]	7.00 [6.00;11.0]	12.0 [11.0;18.0]	0.021
FS (FACIT Fatigue score),+	0.49 (0.006)	17.0 [8.8;23.4]	17.0 [14.0;22.0]	38.0 [28.0;43.0]	0.004
TOI (PWB+FWB+FS),+	0.50 (0.005)	36.8 [25.5;47.0]	37.0 [32.0;45.0]	75.0 [55.0;82.0]	0.001
Pain impact,-	0.08 (0.679)	33.3 [0.00;87.5]	83.3 [66.7;100]	16.7 [0.00;33.3]	0.204
Dyspnoea impact,-	-0.14 (0.474)	33.3 [0.00;75.0]	50.0 [0.00;75.0]	33.3 [0.00;66.7]	0.906
Insomnia impact,-	-0.14 (0.461)	33.3 [0.00;66.7]	33.3 [0.00;66.7]	0.00 [0.00;33.3]	0.380
Appetite loss impact,-	-0.22 (0.233)	50.0 [25.0;75.0]	33.3 [0.00;100]	0.00 [0.00;33.3]	0.312
Constipation impact,-	0.03 (0.863)	33.3 [25.0;100]	66.6 [33.3;100]	33.3 [0.00;100]	0.581
Fatigue impact,-	-0.32 (0.087)	94.4 [58.3;100]	88.9 [66.7;100]	55.6 [33.3;66.7]	0.031
Nausea/Vomiting,-	-0.39 (0.031)	16.7 [0.00;25.0]	0.00 [0.0;16.7]	0.00 [0.00;0.00]	0.025
Physical functioning,+	0.36 (0.052)	16.7 [6.67;36.7]	33.3 [20.0;46.7]	73.3 [33.3;93.3]	0.037
Emotional functioning,+	0.07 (0.712)	50.0 [41.7;70.8]	41.7 [41.7;50.0]	66.7 [50.0;83.3]	0.482
Overall quality of life,+	0.13 (0.489)	41.7 [29.2;54.2]	33.3 [16.7;50.0]	50.0 [50.0;66.7]	0.108

Note: Spearman's rank correlation coefficient with serum 25(OH)D concentrations and its p-value in brackets are shown in the second column. Columns from third to fifth represent the median [first; third quartiles] for each of the 25(OH)D tertiles. The last column shows the Kruskal-Wallis test p-value for the differences between the three groups for each of the analyzed parameters.

Among the patient-reported outcomes, those positively correlated with 25(OH)D were FS (0.49), PWB (0.44) and FWB (0.41). These results were confirmed when partitioning participants according to the tertiles of serum vitamin D levels (Figure 1). A statistically significant negative Spearman's rank correlation was observed with nausea/vomiting (-0.39), although it was due to the high score reported by patients in the first tertile of serum 25(OH)D. Statistically significant associations were also found for the Barthel index, also due to the low score reported by patients in the first tertile of serum 25(OH)D, and for the physical functioning (PF) score and the fatigue symptom impact. Both of the latter associations (lower fatigue impact and higher PF) showed a significantly better score for the third tertile. No statistically significant association was found for the overall quality of life or other symptoms impact assessments or emotional functioning.

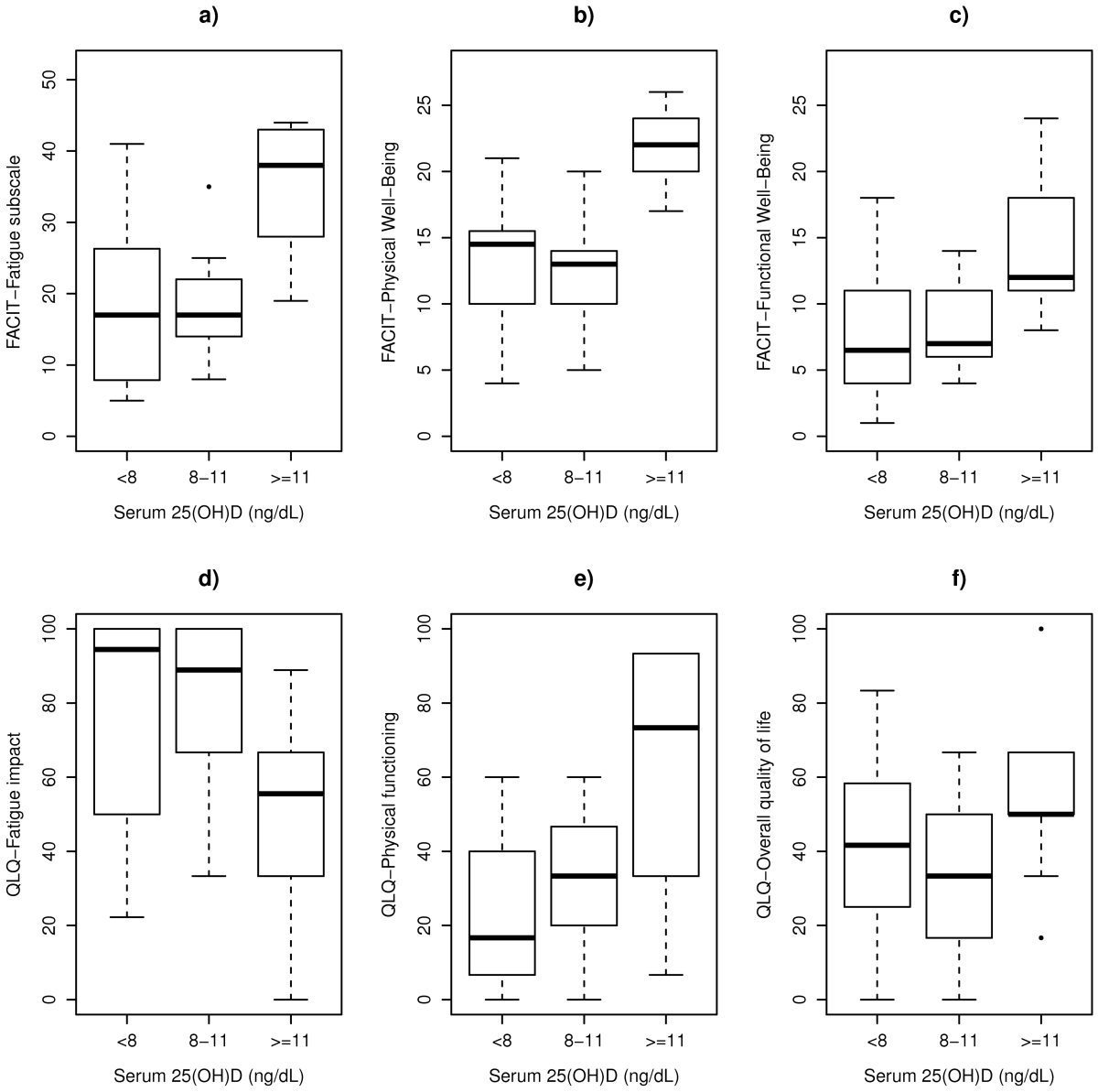

Figure 1. Association between the tertiles of serum 25(OH)D, in ng/dL, and quality of life-related parameters. Boxplot analysis of the association between tertiles of 25(OH)D in the X-axis and patient-reported: a) FACIT-Fatigue subscale score, from 0 to 52, with 52 denoting the best condition; b) FACIT-Physical Well-Being, from 0 to 28, with 28 denoting the best condition; c) FACIT-Functional Well-Being, from 0 to 28, with 28 denoting the best condition; d) QLQ-Fatigue Impact, from 0 to 100, with 0 denoting no impact of fatigue on daily life; e) QLQ-Physical Functioning, from 0 to 100, with 100 denoting excellent physical functioning, and f) QLQ-Overall quality of life, from 0 to 100, with 100 representing a palliative care patient with an excellent quality of life.

Discussion

This study shows that vitamin D deficiency is highly present in patients in palliative care with an advanced solid cancer, who are not severely disabled but are no longer candidates to receiving chemo or radiotherapy. Vitamin D deficiency was estimated to be 90%, with a 95%CI of [73%, 98%]. Two significant positive Spearman correlations were found with serum calcium and phosphorus, both of them expected given vitamin D induction of intestinal calcium and phosphate absorption. A significant negative Spearman correlation was found with triglyceride levels, a finding in agreement with the randomized controlled trial by Muñoz-Aguirre et al [12] in 2014, demonstrating a significant reduction in triglyceride levels after supplementation with vitamin D to postmenopausal women with diabetes. The self-assessment of symptoms placed fatigue as the one with the greatest impact in their lives, above pain, dyspnoea, sleeplessness, appetite loss, constipation, and nausea/vomiting. Fatigue was also the only symptom with a perceived impact significantly correlated with serum 25(OH)D concentrations, which in turn was significantly correlated with the physician's assessment of patients' performance and with patient-reported physical functioning, perceived fatigue as well as with physical and functional well-being. A significant association of 25(OH)D levels with patient-reported overall quality of life or with emotional functioning could not be established.

The main limitation of our findings is the scarce number of patients. Furthermore, given the high heterogeneity of primary tumors included in the study, it is not possible to conduct subanalyses for each primary tumour type. This subanalysis would be important to rule out that the particular type of primary tumor has a direct impact on both the severity of vitamin D deficiency or even on the patient´s perceived quality of life. Nevertheless, this analysis is beyond the scope of this study.

Another limitation is the single-center setting of the patients, which precludes any further extrapolation of our findings, since geographical locations markedly affects both dietary vitamin D intake, and more importantly, sun exposure, both with a great influence on serum 25(OH)D concentrations. However, the geographical influence may be negligible in advanced cancer patients under palliative care as sun exposure is contraindicated before receiving chemo or radiotherapy and also because of their low regular food intake, as they are often malnourished.

There is great variability in the estimated occurrence of vitamin D deficiency among cancer patients. The most recent estimate from Brisbane, Australia, in patients with non-haematological cancer was of 44%. However, the report included patients undergoing both oncological and palliative care [8]. Among advanced cancer patients, estimates of vitamin D deficiency (defined as <20 ng/dL) vary between 47%[9] and 64%[10].

The recent report of a significant positive correlation (measured by Kendall's rank correlation test) between serum vitamin D levels with the Australia-modified Karnofsky Performance Status (AKPS) [8], supports our finding of significant positive correlations of 0.37 with KPS and 0.40 with PPS and serum 25(OH)D levels, as estimated by Spearman's rank correlation coefficients.

In conclusion, our study underscores the importance of correcting vitamin D deficiency in cancer patients under palliative care, as patients with higher serum 25(OH)D levels showed significantly higher scores in patient's reported FS, PF, PWB, and FWB scales, and very low scores of fatigue impact when compared with patients with lower serum 25(OH)D concentrations. To our knowledge this is the first study to report that fatigue is the symptom with the highest impact in advanced cancer patients in palliative care. The translational relevance of this finding is high as it suggests that vitamin D supplementation could reduce fatigue and improve physical and functional status. Although a direct relationship between serum vitamin D levels and quality of life could not be demonstrated, it would be reasonable to speculate that, by reducing fatigue, the health-related quality of life, as perceived by these patients, could be improved. Undoubtedly, only a randomized clinical trial would address this critical issue. To this end, a randomized clinical trial, with EudraCT number 2013-003478-29, has been designed.

Acknowledgments

The authors thank Dr. Montse Rué at the Department of Basic Medical Sciences Department at the University of Lleida for her valuable suggestions and careful reading of the final version of this manuscript.

Ethical standards

This study was approved by Human Study Committee at the Hospital Arnau de Vilanova and has therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. All participants gave their informed consent prior to their inclusion in the study. No detail that might disclose the identity of the participants under study is provided.

Conflict of interest

The authors declare no conflict of interest. The blood chemistries in these patients were part of their regular medical follow-up supported by the Spanish Public Health Care System.

The authors have full control of all primary data and agree to allow the journal to review their raw data if requested.

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6

THE EFFECT ON QUALITY OF LIFE OF VITAMIN D ADMINISTRATION FOR ADVANCED CANCER TREATMENT (VIDAFACT STUDY): PROTOCOL OF A RANDOMISED CONTROLLED TRIAL

Published in:
Martinez-Alonso M, Dusso A, Ariza G, Nabal M. BMJ Open 2014; 4:e006128

According to the NIH Office of Dietary supplements (USA), vitamin D (cholecalciferol) is related to "resistance to chronic diseases (such as cancer and cardiovascular diseases), physiological parameters (such as immune response or levels of parathyroid hormone), and functional measures (such as skeletal health, physical performance and falls)". All of these relationships underscore the potential benefits of cholecalciferol supplementation in cancer. This is the first study designed to obtain conclusive evidence on the effect of cholecalciferol in advanced cancer patients. The main goal is to assess the effects of cholecalciferol supplementation on patient's perceived quality of life. Cholecalciferol impact on fatigue and physical performance will also be assessed, as well as the cost-utility of cholecalciferol supplementation.

Patients satisfying the inclusion criteria will be randomly assigned to receive either cholecalciferol or placebo upon signing an informed consent. Eligible patients will be adults under palliative care for having a locally advanced or metastatic or inoperable solid cancer. Among exclusion criteria will be having a Karnofsky < 30%. This is randomized triple-blind placebo-controlled multicenter trial. The randomization will involve a computer-generated randomization procedure centralized by the coordinating center. The assigned treatment will be allocated by the hospital's pharmacy service in order to warrant that neither patients nor their health care providers know their assigned group. Cholecalciferol (4000IU/day) or placebo will be added to palliative care treatment starting at day 14 and continued up to day 42, with programmed outpatient follow-up visits every 14 days.

BMJ Open

The effect on quality of life of vitamin D administration for advanced cancer treatment (VIDAFACT study): protocol of a randomised controlled trial

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To cite: Martinez-Alonso M, Dusso A, Ariza G, *et al*. The effect on quality of life of vitamin D administration for advanced cancer treatment (VIDAFACT study): protocol of a randomised controlled trial. *BMJ Open* 2014;**4**: e006128. doi:10.1136/bmjopen-2014-006128

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2014-006128).

Received 16 July 2014
Revised 12 November 2014
Accepted 14 November 2014

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ABSTRACT

Introduction: Vitamin D is related to resistance to chronic diseases, physiological parameters and functional measures. All of these relationships underscore the potential benefits of cholecalciferol or D3 (nutritional vitamin D) in cancer. This is the first study designed to obtain conclusive evidence on the effect of cholecalciferol in advanced patients with cancer. The main goal is to assess its effects on the patient's perceived quality of life. Cholecalciferol's impact on fatigue and physical performance, as well as its cost utility, will also be assessed.

Methods and analysis: A randomised triple-blind phase II/III placebo-controlled multicentre trial has been designed. Patients satisfying the inclusion and exclusion criteria will be randomly assigned to receive cholecalciferol or placebo. Eligible patients will be adults with a locally advanced or metastatic or inoperable solid cancer in palliative care, who have given signed informed consent and have matched inclusion and exclusion criteria. The randomisation will be based on a computer-generated procedure and centralised by the pharmacy service of the coordinating centre. The assigned treatment will be administered by the hospital's pharmacy to conceal group allocation for patients and healthcare providers. Cholecalciferol (4000 IU/day) or placebo, starting at day 15 and continuing up to day 42, will be added to palliative care treatment. Outpatient visits will be scheduled every 14 days.

Ethics and dissemination: Ethical approval was received from the Medical Ethical Commitee of the HUAV (CEIC-1169). Participants and their families will receive the research findings which will also be disseminated on local and national media, presented at national and international meetings of the specialty, and published in peer-reviewed scientific journals.

Trial registration number: EudraCT: 2013-003478-29.

Strengths and limitations of this study

- At least a clinically relevant improvement in the quality of life is expected for oncological patients with no possibility of curable treatments.
- It is a multidisciplinary approach to patient care which includes coordination with physiatrists in functional rehabilitation.
- Cost utility analysis of vitamin D supplementation will allow informed decision-making.
- Potential limitations are that the amount of sun exposure, although expected to be low for patients with advanced cancer in palliative care, has not been taken into account.

INTRODUCTION

Background and rationale

Cancer-related fatigue is the most common symptom in patients in palliative care with an overall prevalence of 90% at terminal stages.[1] However, cancer-related fatigue cannot be easily diagnosed, since it may be masked by pain, dyspnoea or nausea.[2] It often becomes apparent once it compromises basic daily life activities.[3] Additionally, there are also subjective, psychological and emotional components of the impact of lack of strength on each individual, which can be appropriately assessed by currently available questionnaires which measure the patient's perception of the impact of fatigue on his/her quality of life.[4 5]

The pathogenesis of cancer-related fatigue is multicausal and involves physiological and biochemical disorders directly associated with tumour progression, severe adverse effects resulting from cancer treatment, as well as physical and psychological stress, anaemia, lack of exercise, chronic pain and severe uncontrolled symptoms.[6 7]

At present, a variety of interventions have been studied with reportedly small but significant benefits such as drug therapy,[8–10] which are not free of adverse effects. Psychosocial and physical interventions on fatigue intensity are also available for patients with cancer.[11] However, in patients in palliative care, recommendations for therapy are scarce. Functional rehabilitation[12] should be

tailored to each patient to help maintain a relatively active daily life. The goal is not to recover a specific level of activity, but to maintain physical endurance so that rest or inactivity will not reduce muscle reserve.

Vitamin D is a fat-soluble vitamin present in only a few foods, but which can be obtained from sun exposure and supplements in its biologically inert form. It must undergo two hydroxylations in the body for activation. First, the liver converts vitamin D to 25-hydroxyvitamin D (25(OH)D), and afterwards the physiologically active 1.25-dihydroxyvitamin D (1.25(OH)2D) is produced mainly by the kidneys.

A recently published review[13] supports numerous reports delineating the multiple mechanisms underlying vitamin D prosurvival actions experimented with at the laboratory. Their findings show that vitamin D deficiency results in a defective control of: (1) Cell growth causing hyperproliferative disorders, genomic instability, Tumour necrosis factor Alpha Converting Enzyme (TACE)-driven metastasis, exacerbated growth and immune escape; and accelerated progression of cancer lesions;[14–17] (2) DNA repair mechanisms causing age-associated disorders and resistance to therapy in cancer;[16 18] (3) Muscular weakness and impaired neuromuscular function;[19 20] (4) Musculoskeletal pain derived from cancer treatment;[21] (5) The immune system causing increased antigenicity in antigen presenting cells, reduced content of T-regulatory lymphocytes, systemic inflammation and multiple organ damage, as well as a higher propensity for autoimmune disorders;[15 19] (6) The integrity of the FGF23/klotho responsible for the antiageing properties of klotho in the kidneys, in protecting the vasculature from atheromatosis and calcification, and as a tumour suppressor and protector from the onset of resistance in cancer treatment;[22–24] (7) The renin-angiotensin system to prevent hypertension, renal and cardiovascular damage due to excessive oxidative stress;[25 26] (8) Acquisition of atherothrombotic phenotype of circulating monocytes-macrophages and increased severity of atherosclerotic lesions;[27] (9) Podocyte function to protect from proteinuria and proteinuria-induced cardiovascular lesions.[28 29]

When no curable treatment is possible, palliative care is directed towards minimising symptoms, relieving suffering and bringing patients to the best possible health-related quality of life (HRQoL). Avoiding the toxicity associated with some palliative treatments is a *must* in these patients. There is an urgent need to develop new interventions in this population based on current evidences, namely: (1) The strong epidemiological association between vitamin D deficiency and the high risk of mortality from all causes in the general population[15] and specifically from cancer;[30 31] (2) The high frequency of vitamin D deficiency in patients with cancer, estimated to be between 47%[32] and 88%;[33] (3) The anticancer, antiageing, antipain, immunomodulatory and the protective renal, cardiovascular and neuromuscular properties of a normal vitamin D status;[15 19 34 35] and (4) The significant 11% reduction in all cause mortality estimated for D3 by combining all randomised controlled trials.[30] We present a clinical trial designed to obtain, for the first time, evidence-based recommendations on the efficacy of vitamin D3 supplementation, a safe, non-costly therapeutic strategy, in improving physical performance, decreasing fatigue and increasing HRQoL in patients with advanced cancer in palliative care.

OBJECTIVES

The primary objective of this study is to evaluate the efficacy of the administration of vitamin D3 to enhance patient-reported HRQoL.

The secondary objectives of this study are: (1) To evaluate the efficacy of the administration of vitamin D3 for enhancing physical performance, decreasing perceived fatigue and achieving serum levels of 25(OH)D above 30 ng/mL; (2) To evaluate the effect on tumour biomarkers; (3) To explore the relationship between vitamin D treatment compliance and 25(OH)D levels; (4) To explore the relationship between 25(OH)D levels and renal function; (5) To explore the dose–response relationship in the group of patients with vitamin D3 for the main outcome; (6) and to assess the cost utility of the proposed administration of vitamin D3.

METHODS AND ANALYSIS

The tolerable upper intake level (UL=4000 IU/day or 100 µg/day) has already been established by the European Food Safety Authority for the adult population.[36] However, there is a need for a proof of concept trial to be conducted in patients with advanced cancer in palliative care to gain preliminary data on the safety and efficacy of high doses (at UL) of vitamin D. Therefore, a phase II proof of concept study is planned to obtain reliable data to support a phase III confirmatory trial, within a randomised controlled trial with a placebo two-stage adaptive design.

Trial design

A randomised triple-blind phase II/III placebo-controlled multicentre trial has been designed. The randomisation will be based on a computer-generated procedure centralised by the pharmacy service of the coordinating hospital in order to ensure the required treatment allocation concealment. Serum levels of vitamin D will be not available for the patients or their physicians to preserve treatment allocation concealment. Randomisation will be stratified by primary solid tumour type in a 1:1 ratio. In a proof of concept trial (phase II or stage 1), patients will be assessed after the first 14 days of treatment about self-perceived changes in HRQoL. The study includes a first interim analysis similar to a futility test to discontinue the trial, and reject vitamin D3, if no better outcome is obtained when compared to the placebo group. Otherwise, it will continue to Phase III (stage 2), which is planned to establish the efficacy in improving and

maintaining HRQoL as well as the safety of the treatment with UL of vitamin D over placebo for 28 days (till day 42 from enrolment). This study will assess the efficacy of vitamin D when administered in combination with the usual palliative care and functional rehabilitation.

Study setting

Phase II of the study will take place at Hospital Universitari Arnau de Vilanova (Lleida, Spain). For phase III of the study, three additional Spanish hospitals, *Duran i Reynalds* (Barcelona), *La Paz* (Madrid) and *Virgen de la Macarena* (Sevilla), will participate.

Patients

Eligible patients will be adults with a locally advanced or metastatic or inoperable solid cancer in palliative care on signed informed consent. Exclusion criteria will be having a Karnofsky <30%, being pregnant or breastfeeding females, undergoing severe liver or renal (glomerular filtration rate <60 ml/min) failure, having a cognitive deterioration (more than 5 mistakes in the Pfeiffer test), suffering from significant pain, dyspnoea, nausea or vomiting (more than 6 out of 10 in the corresponding Numerical Rating Scale 0:10), hypercalcaemia (> 10.5 mg/dL), having received chemotherapy or radiation therapy within the past 3 weeks prior to inclusion, or having the possibility of initiating a new cycle of chemotherapy or radiation therapy within a period of 6 weeks after their inclusion date.

A prescreening day is scheduled for each adult patient with a locally advanced or metastatic or inoperable solid cancer in palliative care who did not present any known reason to be excluded. On that day, a blood test will be ordered (since results should be available on the screening day for the complete assessment of exclusion criteria) and a visit with the physical rehabilition medical doctor will be scheduled for the same day.

On the screening day, those patients satisfying inclusion and exclusion criteria will be provided with complete information about the study and enrolled into the study pon signed informed consent.

Intervention

Vitamin D3 supplements of 4000 IU/day (UL) or placebo will be added to palliative care treatment on day 14 after enrolment and continued up to day 42. Outpatient visits will be scheduled every 14 days. Supportive evidence for the UL established dose[36] is provided by randomised controlled studies in which this quantity or higher was administered to various population groups for up to 12 months without evidence of persistent hypercalcaemia or hypercalciuria.

Palliative care treatment will be standardised among participating physicians to ensure comparable procedures on symptoms control (pain, nausea, vomiting, constipation, diarrhoea, lack of appetite, shortness of breath, cough and dry mouth).

Functional rehabilitation will be coordinated by the rehabilitation doctor at each participating hospital from day 0. On that day, there will be an evaluation of the clinical and functional status (weakness, effort tolerance, mobility, functional performance and independence in activities of daily living), neuro-orthopaedic disorders, orthopaedic aids necessary to improve the functionality and individualised physical therapy to perform. Three additional sessions will be scheduled before day 14 to work in the following basic protocols: Assisted and free active physical therapy; Respiratory physiotherapy; Rehabilitation of trunk balance in sitting and standing; Re-education in walking; Energy saving measures, and teaching family involvement. Any requirement for additional measures of rehabilitation will be specifically noted. Leaflets containing advice and recommended exercises for functional rehabilitation will be provided to all participating patients and their families.

OUTCOMES

Primary outcome

Change in patient self-reported HRQoL is the primary outcome. It will be assessed using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C15-PAL,[37] a questionnaire developed for patients with cancer in palliative care. It includes rates on: pain, physical function, emotional function, fatigue, global health status/quality of life, nausea/vomiting, appetite, dyspnoea, constipation and sleep. Its scale rating *global health status/quality of life* using a numbered scoring scale from 1 or *very poor* to 7 or *Excellent* is the primary outcome. An anchor question approach is included in order to establish ranges of scores reflecting patient self-assessment of changes in perceived HRQoL (as an approach to minimal important difference assessment).

Since patients with advanced cancer in palliative care can undergo rapid health deterioration (within a few days), primary as well as secondary outcomes will be recorded at baseline and on the allocation day (14 days after enrolment) in order to assess intrapatient variability occurring before any intervention. After starting the intervention, primary and secondary outcomes will be collected on days 28 and 42 from enrolment day (after 14 days and 28 days of taking vitamin D or placebo).

Secondary outcomes

Change in cancer-related fatigue is the second most important outcome, and will be assessed with the fatigue subscale of the Functional Assesment of Cancer Therapy:Fatigue (FACT-F) questionnare.[38] FACT-F is a widely used 13-item fatigue subscale where each item is a five-point Likert self-report scale ranging from 0='not at all' to 4='very much so'. The total score varies from 0='worst condition' to 52='best condition'.

Change in functional capacity is another important secondary outcome and will be assessed using the

Barthel Scale,[39] an ordinal scale that measures performance in activities of daily living, as well as the Karnofsky and the Palliative Performance Scale (PPS) scores,[40 41] which are used to quantify patients' performance status. All of them provide a score from 100 to 0, where 100 indicates no evidence of disease (normal performance) and 0 indicates death.

Other secondary outcomes include changes in serum levels of 25-hydroxyvitamin D, changes in tumoural biomarkers, adherence to the randomised intervention (defined by the proportion of compliance with the randomised intervention out of the total 28 days), renal function and cost utility analyses. Utilities will be based on the patient self-reported HRQoL measured by EuroQoL (EQ-5D; 3 L). This questionnaire assesses five dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) to define the health state of patients. Each health state will be translated in the corresponding valuation by applying the Spanish general population utility weights, resulting in valuations from 1 (optimal health) through 0 (as bad as death) to negative values (worse than death). Direct costs will be collected in both groups.

Sample size

The research team considers that a 15% difference is clinically relevant and that differences below 15% will not suffice to demonstrate the clinical significance of the effect of supplementation with vitamin D on quality of life. Therefore, this study is designed to detect differences of 15% or more in the proportion of patients with improved HRQoL between the groups. Error probabilities of α and β to 0.05 and 0.2, respectively, for a unilateral contrast with a 1:1 allocation are fixed for sample size calculations.

The phase II sample size is designed to control early stopping probability based on the exact binomial distribution (Simon, 1989) on optimal two-stage designs and fixed to at least 28 patients per group (optimal design for the first stage). The trial will be stopped if the number of patients that improve is not higher in the intervention group than in the control group.

The total sample size for this study (adding phases II and III) is computed as the minimal number of patients per group to detect differences from 15%, even in the case of maximal requirements that would be having proportions of improvement in HRQoL close to 50%. Therefore, with proportions of improvement in HRQoL of 42.5% for the placebo group and 57.5% for the vitamin D group, and using the same error probabilities in a unilateral contrast, a minimum of 137 patients per group (a total of 274 patients enrolled) are estimated as the minimum sample size required by applying the arcsinus approximation. Since twice this improvement could be observed in the vitamin D group, an interim analysis is scheduled at the end of treatment for the first 43 patients per group (phase II patients included) in order to minimise the number of patients in the placebo group. If the difference in the proportion of patients with minimally improved HRQoL is twice the expected 15% in favour of vitamin D3, the trial will be stopped for ethical reasons for the benefit of the patients in the placebo group. In other words, the second interim analysis is planned with a stopping rule so that if the improvement difference is 30% or greater, all the participants will benefit. Figure 1 summarises this study design.

Assignment of interventions

The randomisation process will be centralised at the Pharmacy Service of the Hospital Universitari Arnau de Vinalova. The Pharmacy Service will be the responsible for randomising and blindly assigning vitamin D3 or placebo to each patient, stratified by the primary tumour and blocking it to ensure the same number of patients in each intervention. Drug or placebo formulation, labelling and allocation will be performed by the pharmacist, who will create an identifier for each patient, independently from the order of entry into the study. The matching of each patient identifier with its allocated intervention will be saved in an independent database for the exclusive use of the pharmacist or the External Safety Monitoring Committee until the end of the study.

Data collection and management

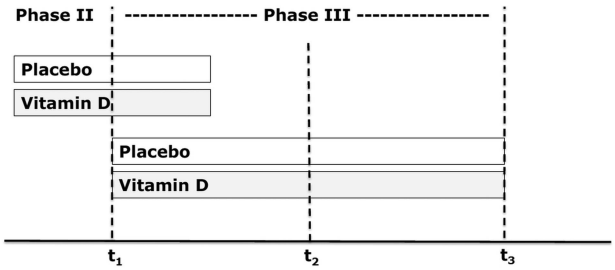
Figure 2 summarises the data collection and management description that is detailed below.

Data collected exclusively at baseline (day 0)

The inclusion and exclusion criteria checklist and baseline information will be also collected including sociodemographical data (age, sex, education), anthropometric data (height), clinical data (primary tumour, stage and treatment), as well as treatments that may interact with vitamin D (antiepileptics, antihypercholesterolaemic, certain diet drugs and corticosteroids).

Data collected at all visits (days 0, 14, 28 and 42)

Collection will include: anthropometric data (weight, body mass index, triceps skinfold); palliative care treatments (cachexia, pain,...); functional capacity (Barthel, Karnofsky, PPS); cancer-related fatigue (FACT-F



t_1: Interim analysis, after 28 patients per arm were assessed till day 28.
t_2: Interim analysis, after 43 patients per arm were assessed till day 42.
t_3: Final analysis, after 137 patients per arm were assessed till day 42.

Figure 1 Trial design.

Figure 2 VIDAFACT participant timeline.

	Pre-screening*	Pre-intervention		Intervention (vit. D or placebo)	
		Day 0 (Enrolment)	Day 14 (Allocation)	Day 28	Day 42
Assessment of available Inclusion and Exclusion criteria	●				
Blood test order	●		●	●	●
Complete assessment of inclusion and Exclusion criteria		●			
Onset of the intervention in physical rehabilitation		●			
Socio-demographical data (age, sex, education)		●			
Antropometrical data (height)		●			
Clinical data (primary tumour, stage and treatment)		●			
Treatments that could interact with vitamin D		●			
Anthropometric data (weight, BMI, tricipital skinfold thickness)		●	●	●	●
Paliative care treatments		●	●	●	●
Biochemical data		●	●	●	●
Functional capacity scales (Barthel, Karnofsky, PPS)		●	●	●	●
Cancer-related fatigue (FACT-F subscale)		●	●	●	●
Health related quality of life (EORTC QLQ-C15-PAL, EQ5D)		●	●	●	●
Patient perceived change in health related quality of life				●	●
Adherence to the randomized intervention				●	●
Safety variables				●	●
Adverse events				●	●

* From 1 to 7 days previous to day 0 (enrolment).

subscale); and quality of life (EORTC QLQ C15 PAL and EQ-5D). Biochemical data will be separated into one part available during the study for the patient and the physician (PCR, total protein, serum albumin, triglycerides and cholesterol (total, low-density lipoprotein, high-density lipoprotein)) and another available during the study only for the external Data Monitoring Committee (25-hydroxyvitamin D, serum calcium and urinary calcium).

Data collected in the postallocation visits (days 28 and 42)

Patient assessment of change from the start of treatment will be collected in response to the question: Please indicate whether there has been any change in your health related quality of life from the start of treatment by choosing one of the following options: −3, very much worse; −2, much worse; −1, slightly worse; 0, no change; 1, a little better; 2, much better; 3, very much better. An at least minimal improvement is defined for patients with an answer from 1 to 3 to this question.

Reported compliance per day starting on day 15 will be also collected.

Most people are not expected to suffer from any side effect, unless they take more than the prescribed amount of vitamin D. Hypercalcaemia and patient assessment of weakness, fatigue, drowsiness, headache, loss of appetite, dry mouth, metallic taste, nausea or vomiting are the adverse events listed in the bibliography. Adverse events will be collected using an ordinal scale of four categories for each one: 'No (0 points)', 'Mild (1 points)', 'Moderate (2 points)' and 'Severe (3 points)'. All adverse events happening postintervention (from 15th to 48th day) will be recorded throughout the study, registering: the adverse event name, starting and ending dates, frequency, severity, intensity, relationship to study drug, action taken and resolution.

Any suspected unexpected serious adverse reaction (SUSAR) will be reported to the Spanish Agency (AEMPS). An SUSAR is defined as any adverse reaction to vitamin D which shows a reasonably and unexpected causal relationship, whose nature, severity or outcome is not consistent with the summary of the characteristics of the technical data and that produces death, endangers the patient's life immediately, produces a persistent or significant disability, requires or prolongs hospitalisation, or becomes a significant danger that is comparable to the above criteria.

Statistical analysis

For the first interim analysis, only the number of patients with at least minimally improved HRQoL will be compared, with no statistical test to base the decision to stop. For the second interim analysis, a difference between response rates of 30% or higher will be used to make the decision to stop. At the end of the study, a descriptive univariate analysis of each group will be performed, followed by a comparison between groups to check if randomisation produced comparable groups in each potential confounder. Bivariate analyses will use the Mann-Whitney or χ^2 test for quantitative or qualitative variables, respectively. In case of differences, analysis of minimally improved HRQoL by logistic regression will be performed adjusting for them. For differences between groups in longitudinal measurements (such as chemistries), linear and non-linear mixed-effect models will be used. Additionally, for the intervention group (patients treated with vitamin D), longitudinal measures of serum vitamin D and renal function will be related by fitting mixed effects linear models. Main outcomes will be analysed by intention to treat. A longitudinal analysis of treatment compliance (cumulative dose in both periods of 14 days) will be performed in relation to serum vitamin D levels as well as an analysis per protocol to look at dose–response effects. Finally, a cost utility analysis of the intervention with cholecalciferol will be performed. For each patient, quality-adjusted life years

will be calculated as the area under the EQ-5D utility curve. Since patients with missing values from questionnaires are likely to be worse than those with the available measurements, the missing outcomes will be imputed using non-linear regression models. A $p<0.05$ will be established as statistically significant. R software will be used.[42]

ETHICS AND DISSEMINATION

Any amendment will be immediately communicated to both agencies. All participants will provide signed informed consent and their confidentiality will be guaranteed by encoding all personal information. Insurance will cover any unexpected damage attributable to participation in the study.

Ethical implications

An external Safety Monitoring Committee has been created, comprised of one physician external to the study from each of the participating hospitals. They will be responsible for monitoring participants' calcium and vitamin D levels during the study in order to ensure the patients' safety and allocation concealment. The research team has no economical interest in favour of or against vitamin D supplementation. Its only interest is to provide evidence as to whether vitamin D supplementation is beneficial or not for patients with advanced cancer in palliative care. Criteria to stop after any of the two planned interim analyses are clearly stablished in the study protocol. After each interim analysis, blindly performed by the statistician of the research team, the pharmacy service will assess the results of interim analyses in relation to the stopping rules established in the protocol and with their exclusive knowledge of the intervention groups. They will be responsible for communicating the end or the continuation of the study based on the criteria established in the study protocol to the research team. The two interim analyses and the phase II/III study design are part of this protocol to minimise the use of time and patients required to demonstrate whether, as hypothesised, there is a clinically significant benefit from the use of vitamin D in patients with advanced cancer in palliative care. The size of the group randomly assigned to placebo is minimised during the study and, if the effect of vitamin D interventions become conclusive,this group will also be supplemented with vitamin D.

Dissemination policy

Given this project's scientific and social interest, its results will be locally and internationally disseminated in congresses, scientific papers and the media.

DISCUSSION

The potentially high scientific and social interests of this project, fully based on the premise that 'When no curable treatment is possible, palliative care should be directed towards minimizing symptoms, relieving suffering and bringing patient to the best possible health related quality of life', can be summarised as follows:

Scientifically:

1. The results of this safe, cost-effective intervention with vitamin D supplementation in patients in palliative care research would be, to the best of our knowledge, the first attempt to conclusively address whether the quality of life for these patients could also improve from the prosurvival properties of a normal vitamin D status, as reported not only in healthy individuals but also in those with diabetes, hypertension, cardiovascular disease, autoimmune disorders, tuberculosis, kidney disease and cancer.
2. This work could provide evidence-based recommendations for the efficacy of vitamin D supplementation to patients in palliative care in improving their quality of life. Such a finding could be immediately incorporated into clinical practice due to its low cost and lack of toxicity. Furthermore, if confirmed, these findings should provide a solid basis for the design of prospective, well-powered clinical trials directed at customising vitamin D supplementation regimens in order to expedite the correction of vitamin D deficiency in treatment-resistant patients and, more importantly, ensure the fast improvement of their quality of life.
3. It could help initiate new lines of research on the pathogenesis of cancer-related fatigue to prevent its onset at early stages and attenuate its progression in cancer.
4. It could bring basic and clinical research together in the arena of advanced cancer.
5. The most optimistic outcome would be to change the 'current paradigm' for patients in palliative care from a state of 'no curable treatment possible' to a vitamin D healing transition making the patient eligible for a new customised cancer therapy with vitamin D as a coadjuvant therapy.

Socially:

1. For the individual: The possibility of giving a patient in palliative care a safe, non-costly, and evidence-based effective option to maintain their quality of life, and the hope that they could eventually become eligible to restart cancer therapy for a cure is invaluable.
2. For the community: This is research with a potentially high clinical relevance, completely independent from the interests of the pharmaceutical industry, whose results could benefit patients in palliative care even in underdeveloped countries with the poorest of healthcare systems.

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Acknowledgements The authors thank Dr Montse Rué at the Basic Medical Sciences Department of the University of Lleida for her valuable suggestions and careful reading of the final version of this manuscript.

Collaborators Josep Porta-Sales; Alberto Alonso; Jaime Boceta.

Contributors MM-A contacted AD, MN and GA to develop the original concept of this study. All authors contributed to discussion and revisions to the study design. MN obtained funding from an organisation with no competing interests. All authors drafted the manuscript, were involved in the revision of the manuscript and agreed on the final approval of the version to be published.

Funding Participants' insurance is covered by a €10 000 donation by Fundación Jesús Serra, from Catalana Occidente.

Competing interests None.

Patient consent Obtained.

Ethics approval Medical Ethical Commitee of the Hospital Universitari Arnau de Vilanova (CEIC-1169).

Provenance and peer review Not commissioned; externally peer reviewed.

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BMJ Open

The effect on quality of life of vitamin D administration for advanced cancer treatment (VIDAFACT study): protocol of a randomised controlled trial

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BMJ Open 2014 4:
doi: 10.1136/bmjopen-2014-006128

Part III

DISCUSSION

7 ABOUT CURRENT RESULTS

This thesis has studied two specific aspects of quality of life related to cancer, one impacting on women attending breast cancer screening, and the other on individuals with advanced cancer in palliative care.

7.1 OVERDIAGNOSIS OF BREAST CANCER

Overdiagnosis affects those women who, in the absence of symptoms, undergo a screening test for breast cancer that detects a tumor which would never have become symptomatic, otherwise. These women are diagnosed and treated for asymptomatic tumors with no progressive potential, and they undergo both unnecessarily invasive tests and intensive treatments. Our model-based estimates of overdiagnosis in Catalonia for the birth-cohorts born from 1935 to 1950 showed an increasing trend from 0.4% to 46.6%. These estimations are associated with the increased use of screening mammography that began in the 1990s in Catalonia.

Kalager et al (Kalager 2012) published a registry-based study that estimated the overdiagnosis of breast cancer in Norway. They compared the incidence of invasive breast cancer from 1996 to 2005 in counties where the screening program was implemented with the incidence in counties where the program was not yet implemented. Two approaches were used with this data, both different from our approach. The estimated rate of overdiagnosis attributable to the program was 18% to 25% ($P < 0.001$) and 15% to 20% ($P < 0.001$) depending on the approach used. Thus, in accordance with our results, mammography screening entails a substantial amount of overdiagnosis.

Carter et al (Carter 2015) conducted a systematic review of the methodology used to quantify and monitor overdiagnosis in cancer in 52 studies, including our study. From the four main estimation methods used, including randomized trials, model-based, pathological and imaging, and ecological and cohort studies, the most appropriate were ecological and cohort studies, because of their possibility to monitor overdiagnosis over a long period of time. To monitor programs is important to maximize the benefits of cancer screening while minimizing harm and cost. The main criticism of the estimates based on mathematical models is the uncertainty about mean sojourn time

in the preclinical state, a parameter that must be included as an input in the model. Sensitivity analyses are required to test the dependability of results from these assumptions. According to this review, only 5 from a total of 21 model-based studies performed a sensitivity analysis.

Our own results of overdiagnosis in breast cancer underscore the importance of striving to meet the ethical responsibility to adequately inform women and help them make screening decisions according to their informed preferences. In this context, Hersch et al (Hersch 2015) investigated whether including information about overdetection of breast cancer in a decision aid would help 50 year old women to make an informed choice about breast screening. They concluded that women can incorporate overdetection information into their reasoning about screening, thereby improving the quality of their decisions.

7.2 QUALITY OF LIFE IN ADVANCED CANCER

Despite the accumulated epidemiological evidence of the high incidence of vitamin D deficiency in oncological patients, a systematic review of all the available literature reports on outcomes from either cholecalciferol or ergoferol supplementation to cancer patients demonstrated the lack of well powered, randomized controlled trials evaluating the efficacy of vitamin D supplementation in correctiong vitamin D deficiency or in improving outcomes.

The few original clinical studies reporting outcomes in cancer patients supplemented with vitamin D_2 or D_3 are very heterogeneous in the vitamin D daily dose used and also in the duration of treatment. A common finding is that the correction of vitamin D deficiency in cancer requires at least of 2,000 IU/day, a dose much higher than the recommended dietary intake. Some researchers support the use of an initial dose of 100,000 IU or 150,000 IU on the first day, followed by 4,000 IU daily, afterwards, to expedite the acquisition of normal vitamin D levels (Cantor 2014). The work by Klapdor et al (Klapdor 2012) is the only publication reporting that doses were personalized to reach and maintain serum vitamin D concentrations over 30 ng/mL in pancreatic cancer patients. Indeed, dose requirements varied as much as from 7,000 IU/week to 140,000 IU/week depending on the patient.

The results of the cross-sectional study presented in this thesis can be considered a proof of concept to conduct the VIDAFACT clinical trial, directed to assess the relationship between correcting serum vitamin D levels (measured by 25(OH)D concentrations) through daily

supplementation with 4,000 IU of cholecalciferol and the quality of life, fatigue and physical and functional performance. Indeed, 90% of the examined 30 advanced cancer patients in palliative care showed vitamin D deficiency. Even a healthy individual with vitamin D deficiency can suffer from bone pain and muscle weakness depending on the severity and the duration of the deficiency. In the cross-sectional study, serum vitamin D concentration was positively correlated with patient-reported absence of fatigue, and physical and functional well-being. From the assessment of the symptoms impact on the perceived well-being, fatigue presented the highest median impact on their lives, rating above pain, dyspnoea, constipation, appetite loss, nausea/vomiting and insomnia. Fatigue was also the only symptom associated with serum vitamin D levels, with lower fatigue in patients with vitamin D concentrations in the upper tertile.

Although in the cross-sectional study there was no direct association between health-related quality of life and vitamin D status, the observed high impact of fatigue on patients' lives, above that of pain, and its correlation with serum vitamin D concentrations, it is reasonable to postulate that increasing serum vitamin D levels to the normal range could further attenuate fatigue, increase muscle strength and improve the quality of life of cancer patients in palliative care.

This thesis includes the design of VIDAFACT, a randomised triple-blind phase II/III placebo-controlled multicentre trial consisting of a safe, inexpensive supplementation with vitamin D to patients in palliative care. The main goal is to conclusively address whether the quality of life of these patients could improve as a result of the reported prosurvival properties of a normal vitamin D status. Additional goals include:

- To provide evidence-based recommendations of the efficacy of vitamin D supplementation in improving the quality of life to patients in palliative care;
- To provide solid basis for the design of prospective, well-powered clinical trials directed to customise vitamin D supplementation regimens to expedite the correction of vitamin D deficiency in treatment-resistant patients;
- To initiate new lines of research on the pathogenesis of cancer-related fatigue to prevent its onset at early stages and attenuate its progression;
- To bring basic and clinical vitamin D research together into the advanced cancer arena;

- To assess whether vitamin D supplementation can change the 'current paradigm' for patients in palliative care from 'no curable treatment possible' to being eligible for a new customised cancer therapy with vitamin D as a coadjuvant therapy.

The achievement of the main goal has high individual and social interests. For the individual, there will be the possibility of receiving a safe, non-costly evidence-based effective option to maintain their quality of life. For society in general, the low cost of cholecalciferol, which makes it independent from the interests of the pharmaceutical industry, offers the possibility of helping advanced cancer patients in palliative care even in countries with the poorest economy.

One of the critiques to the protocol of the VIDAFACT is the use of one dose of cholecalciferol of 4,000 IU/day for 4 weeks rather than the recommended higher dosages, as high as 40,000 IU of D_3 per day and for a longer follow-up of at least 1 year, and preferably 3. The rationale to choose this treatment regimen is the vulnerability of advanced cancer patients in palliative care and also the current upper intake level of vitamin D for healthy adults, established by the European Food Safety Authority. Although it might be possible to use higher doses up to 10,000 IU daily without any risk for the patient, as happens in patients with multiple sclerosis, the safety of such therapeutic strategy has not been tested in patients with advanced cancer under palliative care. Considering their severe weakness and poor general health, it might be counterproductive. Furthermore, cancer often causes hypercalcaemia of malignancy, and hypercalcemia is the main adverse effect of high vitamin D supplementation, with undoubtedly would aggravate the existing hypercalcemia.

Regarding the issue of extending the follow up to 1 year, preferably 3, the main limitation is the frailty of patients with advanced cancer in palliative care, which makes them unable to attend the outpatient clinic or unwilling to undergo blood tests. Furthermore, they are expected to survive no longer than one year. Valuable interventions for these patients are those that will offer improvements in the quality of life, shortly after the initiation of the therapeutic strategy, which was the rationale to examine the efficacy of vitamin D supplementations within four weeks. The 4,000 IU/day may not suffice to correct vitamina D deficiency in 28 days. Nevertheless, in our cross-sectional study, the reduction of the perception of fatigue was observed for values below the normal range.

A main limitation is that a randomized clinical trial makes impossible to personalize dosage to correct vitamin D deficiency, but it could help identify a target concentration in circulation necessary to improve outcomes. Achieving the effective level to improve outcomes,

resulting from this trial, should be the goal to reach in future trials.

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8

FUTURE LINES OF RESEARCH

The results from the research presented by this thesis, open different lines of research:

In breast cancer screening, there is a non-negligible overdiagnosis in Catalonia according to our results. Thus, breast cancer screening is not free of adverse effects that should be well understood in order to design risk-based screening programs for women to have the opportunity of an informed decision to take a screening mammography or not.

Indeed, a line of research entitled *Population participation in decisions and strategies for breast cancer screening* was iniciated with the following objectives: 1) To assess the acceptability, effectiveness and feasibility of a shared-decision making model for the early detection of breast cancer program (EDBCP); 2) To explore the intention of women to participate in a risk-based EDBCP and to evaluate its feasibility in a shared decision making context. Shared decision-making is a model of patient-centered care that enables and encourages people to play a role in the management of their own health. It operates under the premise that, armed with good information, consumers can and will participate in the medical decision-making process by asking relevant questions and expressing personal values and opinions about their conditions and treatment options.The first aim implies to provide complete and up-to-date information to women invited to participate in a screening program. The second aim tries to individually balance the benefits and harms of the early detection of breast cancer.

For cancer patients in general, there is an obvious lack of randomized controlled trials assessing the effect of supplementation with cholecalciferol or ergocalciferol (both of them inactive vitamin D metabolites), in spite of the high prevalence of vitamin D deficiency in cancer patients and the recognized benefits of a normal vitamin D status in the general population. Our preliminary results, from the cross-sectional study on advanced cancer patients in palliative care, show a significant association in the direction of a lower experience of fatigue and higher physical performance and wellbeing for the group of patients in the highest tertile of vitamin D serum levels. Our design of the randomized controlled trial VIDAFACT is an attempt to demonstrate the possible benefits in quality of life, fatigue and physical performance, and wellbeing of supplementing advanced cancer

patients with cholecalciferol. If the future results of this trial confirm our hypothesis, it will open multiple lines of basic and clinical research. The first one will be to establish if there is a dosis-response effect of the supplementation with vitamin D and the serum vitamin D levels associated with patient-reported significant improvement in quality of life and fatigue. No less important will be to determine the best personalized daily dosage of cholecalciferol according to the metabolism capacity of each patient. Thus, identifying patient's characteristics that significantly impact on vitamin D metabolism and transformation into *calcidiol* and its hormonally active metabolite *calcitriol* is needed.

Part IV

CONCLUSIONS

9 MAIN FINDINGS

9.1 BREAST CANCER INCIDENCE AND OVERDIAGNOSIS

1. There has been an increase in the incidence of invasive breast cancer in Catalan women, especially in cohorts born from 1940 to 1955.

2. The highest increase was observed between the ages of 50 to 65 in cohorts born from 1940 to 1955, where the final BC incidence rates more than doubled the initial ones.

3. Dissemination of screening mammography was significantly associated with breast cancer incidence and overdiagnosis.

4. Our model-based estimates of overdiagnosis ranged from 0.4% to 46.6%, for women born from 1935 to 1950, supporting the existence of overdiagnosis of breast cancer screening by mammography in Catalonia.

5. The limited malignant potential of some screening-detected BC tumors may play an important role in overdiagnosis.

6. Given the non-negligible estimated overdiagnosis in Catalonia, women should be clearly informed about the benefits and harms of participating in breast cancer screening.

9.2 VITAMIN D AND CANCER

7. There is no published phase III randomized controlled trial assessing vitamin D (D_2 or D_3) efficacy on patient-reported fatigue, pain or quality of life in advanced cancer patients.

8. Twenty one studies have been included in a systematic review on outcomes in cancer patients after vitamin D_2 or D_3 supplementation. These studies are highly heterogeneous in vitamin

D daily dose and in treatment duration. Nevertheless, it could be extrapolated that to correct serum vitamin D concentrations, vitamin D_3 must be at least 2,000 IU/day, a dose higher than the recommended dietary intake for adults.

9. When assessing the associations between 25(OH)D levels and some aspects measuring the quality of life, as reported herein in cancer patients undergoing palliative care, patients reaching higher circulating concentrations experienced significantly lower fatigue and better physical performance, physical and functional well-being, in comparison to patients with lower serum vitamin D levels.

10. Fatigue is the symptom with the highest perceived impact in advanced cancer patients in palliative care, closely followed by pain.

11. The associations between 25(OH)D and fatigue, physical performance, and physical and functional well-being, in advanced cancer patients in palliative care, support the new trial supplementing patients with vitamin D to reduce fatigue and improve their physical and functional status.

12. A randomised triple-blind phase II/III placebo-controlled multicentre trial has been designed: VIDAFACT, a safe, inexpensive vitamin D supplementation in patients in palliative care, to conclusively address whether the quality of life for these patients could benefit from the pro-survival properties of a normal vitamin D status.