Residential proximity to green spaces and breast cancer risk: the multicase-control study in Spain (MCC-Spain)

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Abstract

Background: Breast cancer is the main cause of cancer mortality among women. Green spaces have been recently associated with reduced cancer mortality among women. Mechanisms explaining the beneficial effect of green spaces include increased levels of physical activity and reduced exposure to air pollution, which have been both associated with cancer development.

Objectives: To investigate the associations between presence of urban green areas, presence of agricultural areas and surrounding greenness and risk of breast cancer, and to assess whether these associations are mediated by physical activity and/or air pollution levels.

Methods: We geocoded the current residence of 1129 breast cancer cases and 1619 controls recruited between 2008-13 in ten provinces of Spain, as part of the MCC-Spain study. We assigned different indicators of exposure to green spaces in a buffer of 300 m, and in nested buffers of 100 m and 500 m around the residence: presence of urban green areas according to Urban Atlas, presence of agricultural areas according to CORINE Land Cover 2006, and surrounding greenness according to the average of the Normalized Difference Vegetation Index. We used logistic mixed-effects regression models with a random effect for hospital adjusting for potential confounders. We explored the effect of several potential effect modifiers. We assessed mediation effect by physical activity and levels of air pollution.

Results: Presence of urban green areas was associated with reduced risk of breast cancer after adjusting for age, socio-economic status at individual and at area level, education, and number of children [OR (95%CI)=0.65 (0.49 – 0.86)]. There was evidence of a linear trend between distance to urban green areas and risk of breast cancer. On the contrary, presence of agricultural areas and surrounding greenness were associated with increased risk of breast cancer [adjusted OR (95%CI)=1.33 (1.07–1.65) and adjusted OR (95%CI)=1.27 (0.92 - 1.77), respectively]. None of the associations observed were mediated by levels of physical activity or levels or air pollution.

Conclusions: The association between green spaces and risk of breast cancer is dependent on land-use. The confirmation of these results in other settings and the study of potential mechanisms for the associations observed are needed to advance the understanding on the potential effects of green spaces on health.

Keywords

Green spaces; breast cancer; physical activity; air pollution; case-control study

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Introduction

Breast cancer is the most common cancer and the main cause of cancer mortality in women worldwide (Ferlay et al., 2013). 25,215 incident cases and 6,075 related deaths are estimated to occur each year in Spain (Ferlay et al., 2013). There are several well established risk factors for breast cancer, such as family-history of first degree relative, benign breast disease, birth of first child after 30 years of age, menarche before 12 years, menopause after 54 years, high endogenous estrogens level, exposure to ionizing radiation, alcohol consumption, higher height, and higher body mass index (post-menopause). Other probable risk factors for breast cancer have been suggested, including reduced physical activity and exposure to air pollutants (Andersen et al., 2017; Hankisnon et al., 2008; Hystad et al., 2015; Mordukhovich et al., 2016).

Green spaces have been associated with improvements in various health outcomes, including psychological well-being, birth outcomes, cardiovascular diseases, and overall mortality (Bowler et al., 2010; Dadvand et al., 2012b; Gascon et al., 2016; Nieuwenhuijsen et al., 2016; Tamosiunas et al., 2014). Few studies have also reported association between green spaces and risk of cancer. Results from a case-control study indicate that surrounding greenness at residence is associated with decreased risk of prostate cancer (Demoury et al., 2016). Results from a large cohort study of women indicate that surrounding greenness at residence is associated with reduced cancer mortality (James et al., 2016). However, research in this area is limited.

Several mechanisms could explain the potential association between exposure to green spaces and risk of breast cancer. Green spaces have been positively associated with increased levels of physical activity (Coombes et al., 2010; McMorris et al., 2014; Richardson et al., 2013) (although this association was not observed in other studies

(Maas et al., 2008; Ord et al., 2013)), and physical activity has been associated with reduced risk of breast cancer in some studies (Lope et al., 2017; Moore et al., 2016; Wu et al., 2013). Green areas tend to have lower levels of air pollution (Dadvand et al., 2012a; Konijnendijk et al., 2013), and air pollution (air pollution as a mixture, and particulate matter specifically) was classified in 2014 as carcinogenic to humans by the International Agency for Research on Cancer (IARC), according on mechanistic and epidemiologic studies (IARC, 2014; Loomis et al., 2013). However, the association between air pollution and breast cancer is not clear (Andersen et al., 2016; Mordukhovich et al., 2016).

Most of these mechanisms however, may stand for green spaces such as parks or forests, but may not for others such as agricultural areas. In fact, residential proximity to agricultural areas has been associated with increased risk of cancer (Camille et al., 2017; Gómez-Barroso et al., 2016).

In the current study, we aimed to evaluate if residential proximity to urban green areas, residential proximity to agricultural areas, and overall greenness surrounding the residence are associated with risk of breast cancer. We also explored whether these associations are mediated by levels of physical activity and/or levels of air pollution.

Methods

Study population. The MCC-Spain study (the multicase-control study in Spain, http://www.mccspain.org/) is a population based multi-case-control study conducted between 2008 and 2013 in different provinces of Spain. The study has been extensively described elsewhere (Castaño-Vinyals et al., 2015). In brief, five cancer types were included in the MCC-Spain study (breast, colorectal, prostate, stomach and chronic lymphocytic leukaemia) using the same series of population controls. The strategy for controls' selection ensured inclusion of at least one control per case from the same catchment area, of the same sex and with an age difference of no more than 5 years (details on selection of population controls is presented in supplementary material, figure S1). Histologically confirmed incident cases of cancer were actively searched in each participating hospital by researchers involved in the study. Patients were contacted just after the diagnosis of cancer was confirmed and were invited to participate in the study. Participating hospitals were the oncologic reference centre from each study area. The inclusion criteria for participants was age between 20-85 years old and residence in the catchment area of the participating hospitals for at least 6 months prior to diagnosis (cases) or recruitment (controls). Exclusion criteria for cases and controls were communication difficulties or physical ability impairment to participate in the interview.

For the current analysis we used breast cancer cases and controls. Inclusion criterion for cases was incident histological confirmed diagnosis of cancer (defined according to the International Classification of Diseases 10th Revision [ICD-10]: C50, D05.1, D05.7) and for controls no history of breast cancer. Overall, seventeen participating hospitals in ten provinces of regions (Asturias, Barcelona, Cantabria, Girona, Guipuzcoa, Huelva, León, Madrid, Navarra and Valencia) recruited breast cancer cases.

In total, 1,738 cases and 1,910 controls accepted to participate and completed the interview. For the current analysis we excluded the following participants: i) those whose current address could not be geocoded, ii) those from catchment areas that recruited only cases or only controls, iii) those from municipalities that recruited only cases or only controls, and vi) those with missing basic information (variables included in table 1; study flow-chart presented in figure 1).

The study was approved by the Ethics Committee of all participating hospitals and primary health centres and it followed the national and international directives on ethics and data protection [declaration of Helsinki and Spanish law on confidentiality of data (Ley Organica 15/1999 de 13 Diciembre de Proteccion de Datos de caracter personal-LOPD)]. All subjects provided written informed consent prior to participation in the study.

Data collection. Study participants were interviewed by study personnel. Information on the following characteristics was recorded in a structured questionnaire: i) lifetime residential history, which included full address and number of years lived in each residence where the participant had lived for at least one year, from age 18 to interview date; ii) socio-demographic factors; iii) lifestyle factors; iv) reproductive history; and v) recreational physical activity during the last ten years. All recreational physical activities reported in the questionnaire were assigned a "Metabolic Equivalent of Task" (MET, a physiological measure of energy expenditure) using the Ainsworth classification of energy costs of physical activities (Ainsworth et al., 1993), which allowed that calculation of MET hour/week. To avoid changes in physical activity caused by onset of disease we excluded data on physical activity in the two years before the interview date. Anthropometric data were obtained after the interview (Castaño-Vinyals et al., 2015).

Residence based information. Residence at time of study enrolment (from now onwards referred in the text as "current residence") of each study participant was geocoded. Levels of air pollution and indicators of degree of urbanization and of socio-economic level were assigned to each residence. We estimated levels of outdoor air pollution using data from the European models developed by Wang et al (Wang et al., 2014). Wang et al used a large data set from 23 European study areas to developed land use regression (LUR) models that allow the estimation of levels of nitrogen dioxide (NO_2) and of particulate matter with an aerodynamic diameter of less than 2.5 µm ($PM_{2.5}$) at independent sites and areas. We assigned indicators of urbanization using data from the European data set on degree of urbanization (DGUR) (European Comission.Eutostat, 2011). The DGUR classifies municipalities into thinly, intermediate and densely populated areas. This classification is based on a criterion of geographical contiguity in combination with a minimum population threshold based on population grid square cells of 1 km^2. For the current study we classified the DGUR in two categories: densely populated areas (i.e. cities) and less than densely populated areas (i.e. towns and suburbs and rural areas). We assigned indicators of socio-economic status in the area of residence based on the Urban Vulnerability Synthetic Index of Socioeconomic Criteria (ISVU-SE) created by Spanish Department of Architecture, Housing and Land Development (Ministry of Public Works (Spain), 2001). The ISVU-SE assigns a value to each census track according to the percentage of: unemployed population in the area, unemployed young population, contingent workers, workers without qualification, and illiterate population. For the current study we generated quintiles of ISVU-SE (population in the highest quintile was population from the most vulnerable areas, population from the lowest quintile was population from the least vulnerable areas).

Exposure to green spaces. Indicators of green spaces were calculated around each participant's address of residence using geographic information systems (GIS; Geospatial Modelling Environment (Version 0.7.3.0) and ESRI ® ArcMap TM 10.0, ArcGIS Desktop 10 Service Pack 4). We used buffers of 300 m based on the European Commission recommendations for selection of indicators of urban green space in health studies (WHO Regional Office for Europe, 2016). Additionally, we used nested buffers (rather than overlapping buffers) at 100 m of the residence, between 100 m and 300 m of the residence, and between 300 m and 500 m of the residence (Browning and Lee, 2017). Figure 2 represents nested buffers used in this study. To study the association between green spaces and risk of breast cancer we focussed in three different exposures: presence of urban green areas in a given buffer, presence of agricultural areas in a given buffer, and surrounding greenness in a given buffer.

To study the association with presence of urban green areas, we used data from Urban Atlas (European Environment Agency, 2006). Urban Atlas classifies land according to land uses and land cover. Its estimates are available for urban zones with more than 100.000 inhabitants. We defined categorical variables based on presence of "urban green areas" (i.e. "public green areas for predominantly recreational use such as gardens, zoos, parks" of at least 0.25 Ha) and/or "forest" (i.e. "forests with ground coverage of tree canopy > 30%, tree height > 5 m, including bushes and shrubs at the fringe of the forest" of at least 1 Ha) in a given buffer around the residence. As the numbers of participants with "no presence of urban green areas within 500 m from the residence" and the number of participants with "presence of urban green areas within 300 m and 500 m from the residence" were small, we merged these two categories and created the following one: "no urban green areas within 300 m" (figure 2).

To study the association with presence of agricultural areas, we used data from CORINE land cover (CLC2006, (European Environment Agency, 2007)). CLC2006 classifies land according to land use and land cover. It has a resolution of 25 Ha (i.e. areas smaller than 25 Ha with a given classification are not represented; instead, the predominant classification in the area is represented) and it is available for all Europe.

We defined categorical variables based on the presence “arable land, permanent crops, pastures and heterogeneous agricultural areas” in a given buffer around the residence. As the numbers of participants with “presence of agricultural areas within 100 m and 300 m from the residence” and with “presence of agricultural areas within 100 m from the residence” were small, we merged these two categories and created the following one: “agricultural areas within 300” (figure 2).

To study the association with surrounding greenness, we estimated the amount of photosyntethically-active greenness in a given buffer around the residence using the Normalized Difference Vegetation Index (NDVI, continuous variable). NDVI is based on land surface reflectance of visible (red) and near-infrared parts of spectrum, derived from the Landsat (http://landsat.usgs.gov/) images at a resolution of 30x30 m. NDVI is an index ranging -1 to 1 where higher positive values indicate more greenness (Weier and Herring, 2000). Negative values of NDVI mainly correspond to water bodies. We excluded large water bodies from the NDVI satellite imagery before data analysis (PHENOTYPE study protocols (http://www.phenotype.eu/en/), so negative values did not affect the final greenness averages. We looked for available cloud-free Landsat TM for the year 2000-2001 images during spring (i.e., the maximum vegetation period for the study region) from the NASA’s Earth Observing System Data and Information System website (EOSDIS, https://earthdata.nasa.gov/). We used data for the years 2000-2001 (depending on availability) to allow for a lag period between exposure and cancer development, and because there were no data before the year 2000 for certain regions.

Statistical analysis. We conducted descriptive analyses of the study population. Logistic mixed-effects regression models with a random effect for hospital were used to estimate association between each exposure (presence of urban green areas, presence of agricultural areas, and surrounding greenness) and breast cancer. The main exposures under study were: i) presence of urban green areas within 300 m from the residence, ii) presence of agricultural areas within 300 m from the residence, and iii) surrounding greenness in a buffer of 300 m around the residence. We conducted additional analyses using nested buffers of 100 m and 500 m (i.e. buffer of 100 m around the residence, buffer between 100 m and 300 m from the residence, and buffer between 300 and 500 m from the residence, figure 2). For surrounding greenness (continuous variable), we reported results for 1 interquartile range (IQR) increase in average NDVI based on the study population in a given buffer. We used Directed Acyclic Graphs (DAGs) to summarize the information on potential confounders and mediators, and identify which of them should be included in the final model (supplementary material, figure S2). We ran basic models adjusted for age and education, and models adjusted for all the identified confounders: age, individual socio-economic status (a score based on parents' economical level, own education and occupational category), quintiles of ISVU-SE, education status (primary or lower versus secondary or higher), and number of children (0 versus 1 or more). We checked collinearity assessing the variance inflation factor in the fully adjusted model (i.e. adjusted for all potential confounders) (Greenland et al., 2016). We explored if physical activity [0 Metabolic Equivalent of Task (METS) hour/week, 0-8 METS hour/week, 8-16 METS hour/week, >16 METS hour/week] or levels of air pollution (continuous levels of $PM_{2.5}$ and NO_2) at the place of residence were potential mediators. First, we assessed if presence of green spaces and surrounding greenness were associated with levels of physical activity using logistic regression models, and if presence of green spaces and surrounding greenness were associated with levels of air pollution using linear regression models. Second, we assessed if physical activity and/or levels of air pollution were associated with risk of breast cancer using logistic regression models.

We considered menopausal status, family history of breast cancer of first degree relatives, degree of urbanization, and individual socio-economic status as potential effect modifiers. These variables were selected *a priori* because they either define major sub-phenotypes of the disease (menopausal status and family history) or can affect levels of exposure to potential mediators (degree of urbanization). We conducted two sensitivity analyses to check consistency of results: i) analysis including only participants who had lived in the current residence at least ten years before study enrolment; ii) analysis including only participants from urban areas with more than 100.000 inhabitants (i.e. participants with information on Urban Atlas available).

Statistical analyses were conducted using Stata version 14 (StataCorp, College Station, TX, USA).

Figure 1. Study flow-chart

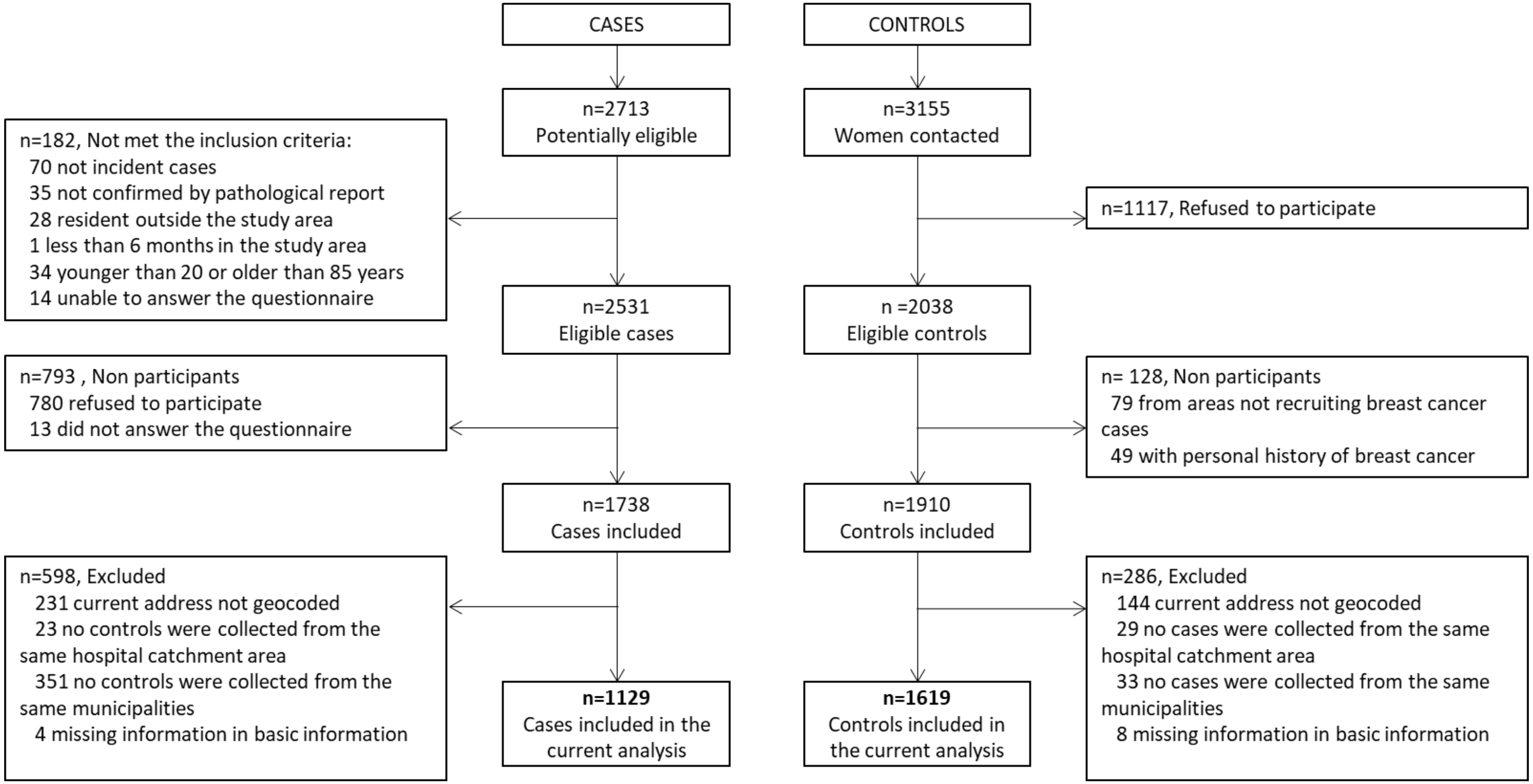
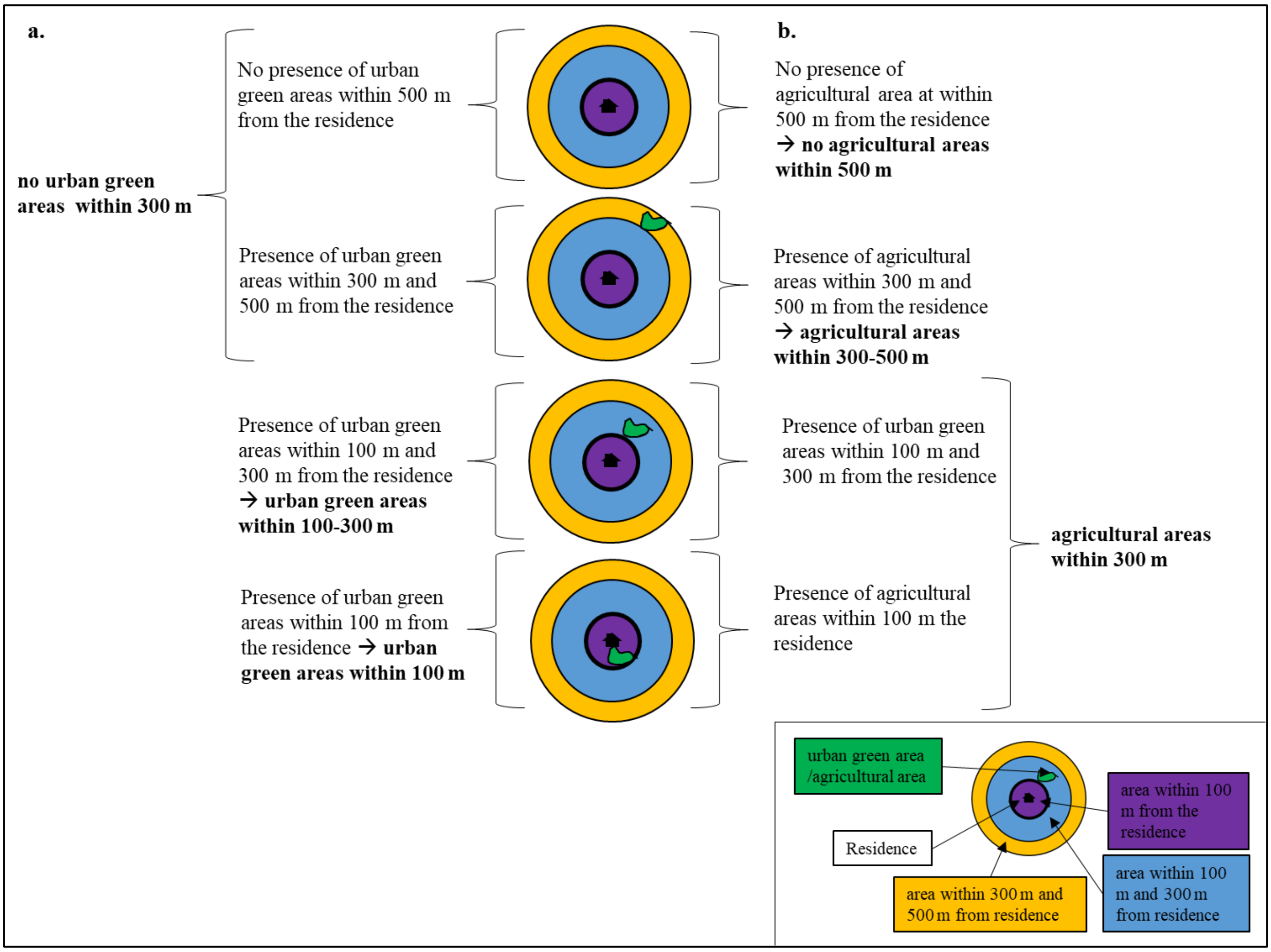


Figure 2. Nested buffers considered to study the association between urban green areas and risk of breast cancer (a.), and between agricultural areas and risk of breast cancer. Labels used to identify each category used in the analyses are indicated with bold front



Results

Study population characteristics. Seventeen hospitals from ten different areas had both breast cancer cases and controls (details of distribution by hospital in supplementary material, table S1). 1129 cases and 1619 controls (65% and 85% of interviewed cases and controls, respectively) were included as they fulfilled the inclusion criteria of the current analysis (figure 1). Compared to excluded cases, included cases were older, and were more likely to be physically inactive, live in densely populated areas, and in the least vulnerable areas (higher ISVU-SE index) (supplementary material, table S2). Compared to excluded controls, included controls were younger, less likely to be overweight or obese, more likely to have family history of breast cancer, have children after 30 years of age more frequently, be smokers, be drinkers, be more physically active, be more educated, live in densely populated areas, and live in the least vulnerable areas (higher ISVU-SE index) (supplementary material, table S3).

Included cases were younger than included controls. Cases had higher mean BMI, were less physically active, and had higher percentage of familiar history of cancer. Cases were more likely to live in more vulnerable areas (i.e. areas with higher urban vulnerability index") compared to controls. Mean levels of $PM_{2.5}$ and of NO_2 were higher among cases. Levels of $PM_{2.5}$ and NO_2 were moderately correlated in the study population (correlation coefficient= 0.532, p-value<0.0001). There were also differences by area/hospital of recruitment between cases and controls (supplementary material, table S1). Seventy-five per cent (2071/2748) of the participants had been living in the current residence at least ten years before study enrolment, and for almost all of them (2069/2071) the duration of the stay in that residence was longer than ten years. For 67% (1855 /2748) of participants the current residence was also the residence where the participant had lived the longest [mean (standard deviation) duration in years = 30 (12)].

Table 1. Characteristics of the study participants

Characteristics	**Control N(%) N=1619**	**Case N(%) N=1129**	**P value**
Exposures			
Presence of urban green within 300 m buffer			
No	165 (14.4)	160 (19.5)	
Yes	977 (85.6)	661 (80.5)	0.003
Presence of urban green area within 300 m buffer			
No	1308 (80.8)	857 (75.9)	
Yes	311 (19.2)	272 (24.1)	0.002
Surrounding greenness (NDVI) within 300 m buffer; median (IQR)	0.22 (0.13)	0.22 (0.14)	0.124
Co-variables			
Age (years); mean(SD)	58.5 (13.1)	56.9 (12.6)	0.001
BMI (Kg/m^2), mean(SD)	25.7 (4.8)	26.1 (5)	0.033
Family history of breast cancer			
No	1468 (90.7)	952 (84.3)	
Yes	151 (9.3)	177 (15.7)	< 0.0001
Menopausal status			
Postmenopausal	1132 (69.9)	740 (65.5)	
Premenopausal	487 (30.1)	389 (34.5)	0.015
Age at menarche (years)			
≤12	672 (41.8)	505 (45.3)	
13-14	734 (45.6)	482 (43.2)	
≥15	202 (12.6)	129 (11.6)	0.196
Number of children			
0	307 (19)	245 (21.7)	
≥1	1312 (81)	884 (78.3)	0.078
Age at first child (years)			
≤30	1049 (80.3)	695 (79.2)	
>30	258 (19.7)	182 (20.8)	0.563
Use of hormonal contraceptives			
Never	812 (50.2)	596 (52.8)	
Ever	807 (49.8)	532 (47.2)	0.166
Use of hormone replacement therapy			
Never	1435 (88.6)	1022 (90.6)	
Ever	123 (7.6)	77 (6.8)	
Not Known (or not remember)	61 (3.8)	29 (2.6)	0.154
Smoking status			

Never	947 (58.5)	626 (55.5)	
Ex-smoker	354 (21.9)	281 (24.9)	
Smoker	317 (19.6)	221 (19.6)	0.156
Alcohol intake, current			
No	529 (36.8)	391 (39.2)	
Yes	909 (63.2)	606 (60.8)	0.224
Alcohol intake, from 30 to 40 years old			
No	526 (36.6)	352 (35.3)	
Yes	912 (63.4)	645 (64.7)	0.520
Night work			
Never	1400 (88.3)	968 (87.2)	
Ever	186 (11.7)	142 (12.8)	0.405
Physical activity			
0 METS h/week	625 (38.6)	514 (45.5)	
0-80 METS h/week	303 (18.7)	189 (16.7)	
80-160 METS h/week	211 (13)	135 (12)	
160 or more METS h/week	480 (29.6)	291 (25.8)	0.004
Education			
Primary or lower	730 (45.1)	526 (46.6)	
Secondary or higher	889 (54.9)	603 (53.4)	0.437
Socio-economic status			
High	295 (18.2)	180 (15.9)	
Low	478 (29.5)	353 (31.3)	
Middle	846 (52.3)	596 (52.8)	0.259
Urban vulnerability index (quintiles)			
1	454 (28)	221 (19.6)	
2	302 (18.7)	194 (17.2)	
3	285 (17.6)	228 (20.2)	
4	340 (21)	266 (23.6)	
5-most vulnerable	238 (14.7)	220 (19.5)	< 0.0001
Degree of urbanization			
Densely populated	1428 (88.2)	995 (88.1)	
Less than densely populated	191 (11.8)	134 (11.9)	0.954
$PM_{2.5}$ (ug/m^3) levels at residence	3.3 (0.6)	3.3 (0.6)	0.008
NO_2 (ug/m^3) levels at residence	3.6 (0.9)	3.7 (0.9)	0.014

* Chi-square test for categorical variables, [§] Kruskal-Wallis test, [#] Student's t-test,

Data on presence of urban green areas (based on Urban Atlas) was not available for participants from areas with less than 100.000 inhabitants (participants from Girona, Guipuzcoa, Huelva, León and certain parts of Cantabria; n=785, 29% of study participants). Data on presence of agricultural areas (based on CLC2006) was available for all study participants. Data on surrounding greenness (based on Landsat images) was not available for participants from isolated areas (n=2, 0.07% of study participants).

As expected, levels of surrounding greenness [median NDVI (IQR)] within the 300 m buffer were higher among participants who had presence of urban green areas than among those who had not in that buffer [0.22 (0.12) versus 0.16 (0.04), p-value = 0.0001]. Similarly, levels of surrounding greenness within the 300 m buffer were higher among participants who had presence of agricultural areas than among those who had not in that buffer [0.33 (0.16) versus 0.20 (0.10), p-value = 0.0001]. Levels of surrounding greenness in relation to presence of urban green areas and of agricultural areas in different nested buffers are presented in supplementary material, table S4.

Green spaces and breast cancer. Eighty three per cent of study participants (81% of cases and 86% of controls) lived within 300 m from urban green areas, and 21% of study participants (24% of cases and 19% of controls) lived within 300 m of agricultural areas. Median (IQR) surrounding greenness (NDVI) within the 300 m buffer was 0.22 (0.13) among study participants [0.22 (0.14) in cases and 0.22(0.13) in controls].

Risk of breast cancer was reduced among participants who had urban green areas within 300 m from the residence compared to those with no urban green areas within that distance [Adjusted OR (95%CI) = 0.65 (0.49 – 0.86); additional adjustment by presence of agricultural areas within 300 m from the residence and levels of surrounding greenness within the 300 m buffer did not change this association, OR (95%CI) = 0.63 (0.47 – 0.84)]. When we looked at nested buffers, we observed that compared to participants who did not have urban green areas within the 300 m buffer, participants who had urban green areas within the 100-300 m buffer had a reduction in risk of breast cancer of about 30%, and participants who had urban green areas within the 100 m buffer had a reduction of breast cancer of about 45% (table 2. See supplementary material table S5, for extended version of this table, including OR (95% CI) for all co-variables in the model). There was evidence of a linear trend of reduced risk of breast cancer among those living closer to urban green areas (p-value for linear trend <0.0001). Results were similar when we considered only participants who had been living in the current residence at least ten years before study enrolment, and when we considered only participants from urban areas with more than 100.000 inhabitants (table 2). There was no interaction between degree of urbanization, menopausal status, family history of breast cancer, or individual socio-economic status, and presence of urban green areas in association with breast cancer (p-value for interaction=0.860, 0.235, 0.571 and 0.309, respectively).

Risk of breast cancer was increased among participants who had agricultural areas within 300 m from the residence compared to those with no agricultural areas within that distance [Adjusted OR (95%CI)=1.33 (1.07–1.65); additional adjustment by presence of urban green areas within 300 m from the residence and levels of surrounding greenness in the 300 m buffer did not change this association, OR (95%CI) = 1.27 (0.92 – 1.77)]. When we looked at nested buffers, we observed that compared to participants with no agricultural areas, participants who had agricultural areas within 300-500 m seemed to have reduced risk of breast cancer. Participants who had agricultural areas within 300 m from the residence (compared to those with no agricultural areas) had an increased risk of breast cancer of about 25%. Results were similar when we considered only participants from urban areas with more than 100.000 inhabitants (table 2. See supplementary material table S5, for extended version of this table, including OR (95% CI) for all co-variables in the model). However, the association was more marked when we included only participants who had been living in the current residence at least ten years before study enrolment (table 2). There was an interaction between presence of agricultural areas and degree of urbanization (p-value for interaction =0.003). In densely populated areas (n= 2,423), the association between agricultural areas and increased risk of breast cancer was stronger than the association found in the overall population. On the contrary, in less than densely populated areas (n=325), there was no association between agricultural areas and risk of breast cancer (table 3). There was no interaction between menopausal status, family history of breast cancer or individual socio-economic status and presence of agricultural areas in association with breast cancer (p-value for interaction=0.219, 0.195, and 0.850, respectively).

Surrounding greenness within the 300 m buffer was associated with increased risk of breast cancer [Adjusted OR (95%CI) per 1-IQR=1.20 (1.07 - 1.34); additional adjustment by presence of urban green areas and presence of agricultural areas within the 300 m buffer did not change this association, OR (95%CI) per 1-IQR = 1.19 (1.00 – 1.41)]. Results were similar for all nested buffers considered (table 2. See supplementary material table S5, for extended version of this table, including OR (95% CI) for all co-variables in the model). The association was more marked when we included only participants who had been living in the current residence at least ten years before study enrolment, and when we included only participants from urban areas with more than 100.000 inhabitants. There was an interaction between surrounding greenness and family history of breast cancer (p-value for interaction = 0.007). Surrounding greenness was a risk factor for breast cancer regardless of family history of breast cancer, but the association was more marked for participants with family history of breast cancer [no family history of breast cancer: n=2420, OR (95%CI) per 1-IQR=1.14 (1.01-1.29); family history of breast cancer: n=328, OR (95%CI) per 1-IQR =1.69

(1.19-2.40)]. There was also an interaction between surrounding greenness and degree of urbanization (p-value for interaction = 0.028). In densely populated areas (n= 2,423), the association between surrounding greenness and increased risk of breast cancer was more marked than the association observed in the overall population. On the contrary, in less than densely populated areas (n=325), there was no association between surrounding greenness and risk of breast cancer (table 3). There was no interaction between menopausal status or individual socio-economical level and surrounding greenness in association with risk of breast cancer (p-value for interaction = 0.147 and 0.175, respectively).

Table 2. Associations between presence of urban green areas, presence of agricultural areas, and surrounding greenness in a given buffer around the current residence, and risk of breast cancer among the overall study population, among participants who had lived in that same residence at least ten years before study enrolment, and among participants from urban areas with more than 100.000 inhabitants

	All population (current residence geocoded), n= 2,748				**Participants who have lived in the current address at least ten years before study recruitment, n=2,082**			**Particpants from urban areas with more than 100.000 inhabitants (data on Urban Atlas available); n=1,963**		
Exposure	control N (%)/ median (IQR)	case N (%)/ median (IQR)	OR (95% CI) *	Fully adjusted OR (95%CI) ±	control N (%)/ median (IQR)	case n (%)/ median (IQR)	Fully adjusted OR (95%CI) ±	control n (%)/ median (IQR)	case n(%) n (%)/ median (IQR)	Fully adjusted OR (95%CI) ±
Presence of urban green areas within 300 m										
No	165 (14)	160 (19)	1.00 (ref)	1.00 (ref)	126 (14)	109 (18)	1.00 (ref)	165 (14)	160 (19)	1.00 (ref)
Yes, within 100 - 300 m	482 (42)	379 (46)	0.71 (0.53-0.95)	0.71 (0.53-0.96)	370 (42)	279 (47)	0.79 (0.56-1.11)	482 (42)	379 (46)	0.71 (0.53-0.96)
Yes, within 100 m	495 (43)	282 (34)	0.53 (0.39-0.72)	0.56 (0.41-0.76)	384 (44)	208 (35)	0.61 (0.43-0.88)	495 (43)	282 (34)	0.56 (0.41-0.76)
Presence of agricultural areas within 500 m										
No	1103 (68)	743 (66)	1.00 (ref)	1.00 (ref)	870 (69)	539 (66)	1.00 (ref)	881 (77)	636 (77)	1.00 (ref)
Yes, within 300 -500 m	205 (13)	114 (10)	0.85 (0.65-1.11)	0.79 (0.6-1.04)	160 (13)	79 (10)	0.78 (0.56-1.07)	136 (12)	65 (8)	0.63 (0.45-0.89)
Yes, within 300 m	311 (19)	272 (24)	1.35 (1.08-1.69)	1.25 (0.99-1.56)	225 (18)	198 (24)	1.51 (1.15-1.99)	125 (11)	120 (15)	1.29 (0.96-1.75)
Surrounding greenness in each buffer #										
100 m	0.19 (0.11)	0.20 (0.12)	1.14 (1.04-1.25)	1.17 (1.06-1.28)	0.19 (0.11)	0.21 (0.12)	1.25 (1.11-1.4)	0.18 (0.09)	0.19 (0.11)	1.21 (1.06-1.37)
within 100 - 300 m	0.22 (0.13)	0.22 (0.14)	1.16 (1.04-1.29)	1.17 (1.04-1.3)	0.22 (0.13)	0.23 (0.14)	1.28 (1.12-1.47)	0.21 (0.11)	0.21 (0.12)	1.22 (1.04-1.43)
within 300 - 500 m	0.24 (0.16)	0.24 (0.17)	1.17 (1.02-1.35)	1.17 (1.02-1.34)	0.24 (0.15)	0.24 (0.17)	1.27 (1.07-1.5)	0.22 (0.13)	0.21 (0.13)	1.25 (1.03-1.52)

IQR: Interquartile range; [*] Basic model, adjusted for age; [±] Fully adjusted model, adjusted for adjusted for age, education, individual socioeconomic status (low, middle, high), area level socioeconomic status (quintiles) and number of children (0 verus ≥1); [#] Increase is per 1 IQR based on the NDVI on all the study population in a given buffer.

Table 3. Associations between presence of urban green areas, presence of agricultural areas, and surrounding greenness in 300 m buffer around the current residence and risk of breast cancer according to degree of urbanization

	Densely populated areas, 2423 (88%)		**Less than densely populated areas, 325 (12%)**	
Exposure	**n (%)/median (IQR)**	**OR (95% CI)** [±]	**n (%)/median (IQR)**	**OR (95%CI)** [±]
Presence of urban green area at 300 m buffer				
No	321 (17)	1.00 (ref)	4 (4)	1.00 (ref)
Yes	1545 (83)	0.66 (0.5-0.88)	93 (96)	0.22 (0.02-2.7)
Presence of agricultural area at 300 m buffer				
No	2099 (87)	1.00 (ref)	66 (20)	1.00 (ref)
Yes	324 (13)	1.65 (1.27-2.14)	259 (80)	0.72 (0.37-1.4)
Surrounding greeness (NDVI) at 300 m buffer; median (IQR) [#]	0.21 (0.11)	1.36 (1.19-1.56)	0.34 (0.16)	0.96 (0.72-1.29)

IQR: Interquartile range; [±] Model adjusted for adjusted for age, education, individual socioeconomic status (low, middle, high), area level socioeconomic status (quintiles) and number of children (0 verus ≥1); [#] Increase is per 1 IQR based on the NDVI on all the study population in 300 m buffer.

Potential mediation effect by physical activity and air pollution.

Presence of urban green areas within 300 m from the residence was no associated with physical activity [OR (95%CI)=0.87 (0.59 – 1.29)]. On the contrary, presence of agricultural areas within 300 m from the residence was associated with increased levels of physical activity [OR (95%CI) = 1.43 (1.06 – 1.95)]. Similarly, surrounding greenness within the 300 m buffer was also associated with increased levels of physical activity [OR (95%CI) =1.16 (1.00– 1.35)]. On the other hand, physical activity was associated with decreased risk of breast cancer [OR (95%CI) adjusted for age, socioeconomic level at individual and area level, education, and number of children=0.92 (0.87 – 0.98)].

Presence of urban green areas within 300 m from the residence was associated with increased levels of $PM_{2.5}$ [β coefficient (95%CI) = 0.30 (0.09 – 0.51) µg/m^3] but not associated with levels of NO_2 [β coefficient (95%CI) = -0.72 (-1.71 – 0.26) µg/m^3]. On the contrary, presence of agricultural areas within 300 m from the residence was associated with decreased levels of both $PM_{2.5}$ and NO_2 [β coefficient (95%CI) = -0.52 (-0.66 - -0.37) µg/m^3 and -6.65 (-7.38 - -5.93) µg/m^3, respectively]. Surrounding greenness was also associated with decreased levels of $PM_{2.5}$ and NO_2 [β coefficient (95%CI) = -0.41 (-0.48 - -0.35) µg/m^3 and -3.38 (-3.62 - -2.94) µg/m^3, respectively]. $PM_{2.5}$ levels were not associated with risk of breast cancer [Adjusted OR (95%CI) for 5 µg/m^3, = 1.15 (0.93 – 1.43)], whereas NO_2 levels were associated with increased risk of breast cancer [Adjusted OR (95%CI) for 10 µg/m^3 1.13 (1.02 – 1.27), respectively].

Inclusion of these potential mediators in the model did not reduce the effect of green spaces on risk of breast cancer, suggesting that none of them mediated the association (table 4). Therefore, we did not conduct a detailed mediation analysis.

Table 4 . Mediation effect of physical activity, $PM_{2.5}$ levels and NO_2 levels of the association between presence of urban green areas, presence of agricultural areas, and surrounding greenness in 300 m buffer around the current residence and risk of breast cancer

	Adjusted OR (95%CI) [±]	Adjusted+PA OR (95%CI) [¥]	Adjusted+$PM_{2.5}$ OR (95%CI) [§]	Adjusted+NO_2 OR (95%CI) [¶]
Presence of urban green area at 300 m buffer				
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	0.65 (0.49-0.86)	0.65 (0.49-0.86)	0.65 (0.49-0.87)	0.66 (0.50-0.88)
Presence of urban green area at 300 m buffer				
No	1.00 (ref)	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	1.33 (1.07-1.65)	1.36 (1.10-1.69)	1.40 (1.12-1.74)	1.63 (1.28-2.06)
Surrounding greeness (NDVI) at 300 m buffer; median (IQR) [#]	1.20 (1.07-1.34)	1.21 (1.08-1.36)	1.25 (1.11-1.40)	1.30 (1.16-1.47)

IQR: Interquartile range; PA: physical activity. [±] Fully adjusted model, adjusted for age, education , individual socio-economic status (low, middle, high), area level socio-economic status (quintiles) and number of children (0 verus ≥1); [¥] Fully adjusted model including physical activity (inactive versus active); [§] Fully adjusted model including levels of $PM_{2.5}$ (continuous variable); [¶] Fully adjusted model including levels of NO_2 (continuous variable); [#] Increase is per 1 IQR based on the NDVI on all the study population in 300 m buffer.

Discussion

We investigated the association between green spaces and risk of breast cancer. Presence of urban green areas (e.g. gardens, zoos, urban parks) around the residence were associated with reduced risk of breast cancer. On the other hand, presence of agricultural areas (e.g. agricultural areas, semi-natural areas and wetlands) was associated with increased risk of breast cancer. Surrounding greenness around the residence also seemed to be associated with increased risk of breast cancer. These findings were consistent when the analysis was restricted to participants who had been living in that same residence at least ten years before study enrolment, and to participants from large urban areas (urban areas with more than 100.000 inhabitants).

Living close to urban green areas was a protective factor for breast cancer, and results suggested a linear trend between distance to green spaces and reduced risk of breast cancer. However, we did not measure the real distance between the residence and the green areas (we did not take into consideration the street network or physical barriers such as major roads, railways and rivers to calculate the distance) and therefore this trend has to be interpreted with caution. Our initial hypothesis was that any potential protective association between green spaces and breast cancer would be mediated by increased levels of physical activity or by reduced levels of air pollution in such areas. However, our results did not support mediation by those factors. First, levels of physical activity were similar regardless of the presence of urban green areas around the residence. Other studies have reported lack of association between green areas and physical activity and it has been suggested that this association might be affected by specific characteristics of the green area (e.g. safety, weather, etc) and the population (e.g. age, social class, etc) under study (Maas et al., 2008; Ord et al., 2013). However, lack of association could be also explained by one of the main limitations of our study. Information of physical activity was self-reported and referred to time spent in leisure time activities between 12 and two years before study enrolment (i.e. ten years period; two years before study enrolment were not considered to avoid changes in patterns due to onset of disease among cases). The length of the period of interest may have affected the accuracy of the information provided. Also accuracy of such information might have been different between cases and controls. Second, people living within 300 m from urban green areas were exposed to higher levels of $PM_{2.5}$ and to similar levels of NO_2 than people living further away from urban green areas. Several studies have shown that vegetation can reduce levels of $PM_{2.5}$, and even more markedly, levels of NO_2 (reviewed by (Hartig et al., 2014)). Nevertheless, it has been hypothesised that certain features of the vegetation, especially in urban settings, may limit air movements promoting accumulation or air pollutants in such settings (Hartig et al., 2014). Another potential explanation for the higher levels of air pollution observed in urban green areas is that Urban Atlas classification includes areas that might not be necessarily covered by vegetation, such as urban parks, in the category of “urban green areas”. Also, in some cities, “urban green areas” are located in central parts of the city where levels of air pollution tend to be higher, while private gardens and green backyards (which are not counted as “urban green areas” in Urban Atlas) are more frequent suburbs where levels of air pollution tend to be lower.

Results from this study suggest that other mechanisms (rather than physical activity or air pollution) may mediate the association between urban green spaces and risk of breast cancer. Mental health and stress restoration could be potential mediators. Few studies have focussed on the association between green spaces and depression (Reklaitiene et al., 2014; Triguero-Mas et al., 2015). Reklaitiene et al. reported reduced prevalence of depressive symptoms in people living closer to a park compared to those living further away, but only among those who spend 4 hours or more per week in the park. Triguero-Mas et al. reported lower self-reported intake of antidepressants and frequency of anxiety and/or depression symptoms among those living in greener areas (i.e. higher levels of surrounding greenness) and among those living within 300 m from green areas (Triguero-Mas et al., 2015). On the other hand, episodes of major depression, diagnosed using the DSM-III criteria (a methods validated by the American Psychiatric Association), have been associated with increased risk of all types of cancer in a prospective study that followed more than 3,000 participants for 24 years (Gross et al., 2010). Increased risk was also suggested when the authors assessed risk specifically for breast cancer. The evidence is limited and no biological mechanisms have been proposed to explain this association, but the potential mediation effect of mental health, and specifically in depression, warrants further evaluation in prospective studies using objective methods to diagnose depression.

In our study, living between 300 m and 500 m seemed to be associated with decreased risk of breast cancer, whereas living within 300 m from an agricultural areas was associated with increased risk of breast cancer. Two recent case-control studies (Camille et al., 2017; Gómez-Barroso et al., 2016) reported increased cancer risk among those living close to agricultural areas. Gómez-Barroso et at, reported higher risk of different types of cancers among children living close to agricultural areas in Spain (Gómez-Barroso et al., 2016). Camille et al, reported higher risk of meningioma among adults living close to open crops in France (Camille et al., 2017). These associations could be explained by higher exposure to pesticides of those living close to agricultural areas. A cohort study conducted also in France following more than 181,842 agricultural workers, reported higher risk of central nervous system cancers, including meningioma, among pesticide applicators (Piel et al., 2017). Several toxicological and epidemiological studies have reported increased risk of breast cancer among women exposed to pesticides (Kim et al., 2016). Density of pesticides use in agricultural areas has been correlated with indoor levels of pesticides in residences located around agricultural areas (Gunier et al., 2011), suggesting that residential distance to agricultural areas may indeed be used as a proxy measure of exposure to pesticide. The protective effect observed among those living between 300 m and 500 m of an agricultural area, could indicate that beyond a given distance, people could benefit from the presence of agricultural areas (through mechanisms similar as those suggested for urban green areas) without the risks associated to pesticides exposures. Nevertheless, these results should be corroborated in other studies designed specifically to evaluate the risks and benefits of living close to agricultural areas.

Surrounding greenness was associated with increased risk of breast cancer. Surrounding greenness is a general measure that combines greenness from different green areas (urban green areas, agricultural areas amongst others) and from sparse vegetation. The positive association between surrounding greenness and risk of breast cancer might be driven by the positive association between agricultural areas and risk of breast cancer, as levels of greenness (median NDVI) were higher in agricultural areas than in urban areas.

Our study has several strengths. Both, exposure and outcome were based on objective information (estimation of exposure to green spaces was based on address at time of study enrolment and definition of outcome was based on histologically confirmed diagnosis of cancer), eliminating the risk of recall bias in the study. We had detailed information on residential history. This allowed us to perform sensitivity analyses including only participants who had been living in the residence at time of diagnostic/study enrolment for at least ten years, avoiding misclassification of cases that might have moved closer to the hospital where they receive treatment after diagnostic. We did have detailed information of demographics and life-style factors which allowed for control of potential confounders. The measurement of different types of green spaces allowed the generation of hypotheses on how different types of green areas can be associated with breast cancer. However, information on detailed features of the green spaces (accessibility, services, types of crops, etc.) and actual use of green space was missing. This information would be helpful to understand the association between green spaces and health. The study has some other limitations. There were differences between cases included and cases not included in the study, and between controls included and controls not included in the study, suggesting that selection of participants could have been biased. Most of these differences were related to socio-economic factors. There were also differences regarding socio-economic factors between cases and controls, despite the use of community controls randomly selected from the same catchment area than cases. Adjustment for individual socio-economic status and socio-economic level in the area of residence made little difference in the association under study. This suggests that differences in socio-economic status between included/not included participants, and between cases and controls, are not likely to have affected our results. Nevertheless, we cannot rule out the effect of residual confounding. Whereas recall bias, might have not affected the association between green spaces and risk of breast cancer, it might have affected the mediation analysis by physical activity (for reasons explained above).

Conclusions

To our knowledge this is the first study focusing on the association between green spaces and breast cancer. We observed a reduced risk of breast cancer among women living close to urban green areas, and increased risk of breast cancer among women living close to agricultural areas, indicating that the association between green spaces and breast cancer may depend on land-use. Confirmation of these results in other settings and specially the evaluation of potential mechanisms are needed to advance our understanding on the potential beneficial effects of green spaces in health.

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