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Cancer mortality in towns in the vicinity of installations for the production of cement, lime, plaster, and magnesium oxide

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Abbreviations:

IPPC: Integrated Pollution Prevention and Control

E-PRTR: European Pollutant Release and Transfer Register

NSI: National Statistics Institute

RRs: Relative risks

95% CrIs: 95% credible intervals

BYM: Besag, York and Mollié

INLAs: Integrated nested Laplace approximations

PAHs: Polycyclic aromatic hydrocarbons

Abstract

Our objective was to investigate whether there might be excess cancer mortality in the vicinity of Spanish installations for the production of cement, lime, plaster, and magnesium oxide, according to different categories of industrial activity. An ecologic study was designed to examine municipal mortality due to 33 types of cancer (period 1997-2006) in Spain. Population exposure to pollution was estimated on the basis of distance from town to industrial facility. Using spatial Besag-York-Mollie regression models with Integrated Nested Laplace approximations for Bayesian inference, we assessed the relative risk of dying from cancer in a 5-kilometer zone around installations, analyzed the effect of category of industrial activity according to the manufactured product, and conducted individual analyses within a 50-kilometer radius of each installation. Excess all cancer mortality (relative risk, 95% credible interval) was detected in the vicinity of these installations as a whole (1.04, 1.01-1.07 in men; 1.03, 1.00-1.06 in women), and, principally, in the vicinity of cement installations (1.05, 1.01-1.09 in men). Special mention should be made of the results for tumors of colon-rectum in both sexes (1.07, 1.01-1.14 in men; 1.10, 1.03-1.16 in women), and pleura (1.71, 1.24-2.28), peritoneum (1.62, 1.15-2.20), gallbladder (1.21, 1.02-1.42), bladder (1.11, 1.03-1.20) and stomach (1.09, 1.00-1.18) in men in the vicinity of all such installations. Our results suggest an excess risk of dying from cancer, especially in colon-rectum, in towns near these industries.

Key Words: Cancer mortality; cement plants; lime plants; industrial pollution; INLA; BYM model

1. Introduction

Cement, lime and plaster are basic materials used for building and construction, whereas magnesium oxide is mainly used in the steel and refractory industry. During the last decades the constant increase in the construction sector has been reflected in an increase in the production of these materials in Europe (European Commission, 2014), with possible consequences in the health of the population, inasmuch as installations for the production of cement, lime, plaster, and magnesium oxide generate and release toxic emissions and waste into the environment – many of them known or suspected carcinogens, such as arsenic, chromium, and dioxins – that can pose a health problem to neighboring towns.

Some studies have linked exposure to emissions of cement plants with health risks (Schuhmacher et al., 2004), and specific health outcomes as contact dermatitis (Isikli et al., 2003), risk of hospital admission for cardiovascular or respiratory causes (Bertoldi et al., 2012), and preterm delivery (Yang et al., 2003) among populations residing in its vicinity. To our knowledge, very few epidemiologic studies focused on cancer have been conducted on populations living near cement clinker plants (excluding cement asbestos industries). With respect to installations for the production of lime, plaster and magnesium oxide there are hardly any epidemiologic studies on these installations' health effects on the populations of nearby towns, even though they are known to generate carcinogenic waste, such as mineral oils and materials containing asbestos (European Environment Agency (EEA), 2015). Great interest therefore lies in assessing the possible relationship between these pollutant industries and the frequency of cancer in their environs.

In relation to pollution sources, the European Commission passed the Integrated Pollution Prevention and Control (IPPC) in 2002 and the European Pollutant Release and Transfer Register (E-PRTR) in 2007. IPPC and E-PRTR records constitute an inventory of geo-located industries with environmental impact in Europe, which is a valuable resource for monitoring industrial pollution, and

renders it possible for the association between residential proximity to such installations and health impacts, such as cancer, to be studied (Fernandez-Navarro et al., 2012; Lopez-Abente et al., 2012).

Hence, the aims of this paper were to: (1) assess possible excess mortality due to 33 types of cancer among the Spanish population residing in the vicinity of installations for the production of cement, lime, plaster, and magnesium oxide governed by the IPPC Directive and E-PRTR Regulation; (2) analyze this risk according to the different categories of industrial activity, and for each installation individually; and, (3) perform analyses for the population, both overall and by sex.

2. Materials and methods

We designed an ecologic study to examine the association between cancer mortality and proximity to installations for cement, lime, plaster, and magnesium oxide manufacturing industries at a municipal level (8,098 Spanish towns), over the period 1997-2006. Separate analyses were performed for the overall population and for each sex.

2.1 Mortality data

Observed municipal mortality data were drawn from the records of the National Statistics Institute (NSI) for the study period, and corresponded to deaths due to 33 types of cancer (see Supplementary data, Table 1). Expected cases were calculated by taking the specific rates for Spain as a whole, broken down by age group (18 groups: 0-4, ..., 80-84 years, and 85 years and over), sex, and five-year period (1997-2001, 2002-2006), and multiplying these by the person-years for each town, broken down by the same strata. Person-years for each quinquennium were calculated by multiplying the respective populations by 5 (with data corresponding to 1999 and 2004 being taken as the estimator of the population at the midpoint of the study period).

2.2 Industrial pollution exposure data

Population exposure to industrial pollution was estimated by reference to the distance from the centroid of town of residence to the industrial facility. We used the industrial database IPPC+E-PRTR provided by the Spanish Ministry for Agriculture, Food & Environment in 2009. Bearing in mind the minimum induction periods for the tumors targeted for study, generally 10 years for solid tumors and 1 year for leukemias (United Nations Scientific Committee on the Effects of Atomic Radiation, 2006), two industry databases were used:

- a) for the study of leukemias, we selected the 67 installations corresponding to IPPC category 3.1, which came into operation prior to 2002 (1 year before the mid-year of the study period), denominated "pre-2002 installations"; and,
- b) for the remaining tumors, we selected the 60 installations corresponding to IPPC category 3.1 which came into operation prior to 1993 (10 years before the mid-year of the study period), denominated "pre-1993 installations".

The year of commencement of the respective industrial activities was provided by the industries themselves.

Each of the installations was classified into one of the following 4 categories of industrial activities, according to the type of manufactured product:

1. "*Cement*": production of cement clinker (43 pre-2002 and 38 pre-1993 installations);
2. "*Lime*": production of lime (18 pre-2002 and 16 pre-1993 installations);
3. "*Plaster*": production of plaster (4 pre-2002 and 4 pre-1993 installations); and
4. "*Magnesium oxide*": production of magnesium oxide (2 pre-2002 and 2 pre-1993 installations);

Owing to the presence of errors in the initial location of industries, the geographic coordinates of the industrial locations recorded in the IPPC+E-PRTR 2009 database were previously validated: every single address was meticulously checked using Google Earth, the Spanish Agricultural Plots Geographic Information System (Spanish Ministry of Agriculture and Food and Environment, 2015), the GoogleMaps server, the "Yellow pages" web page, and the web pages of the industries themselves, to ensure that location of the industrial facility was exactly where it should be.

2.3 Statistical analysis

Three types of analysis were performed to assess possible excess cancer mortality in towns lying "near" versus those lying "far" from cement, lime, plaster, and magnesium oxide manufacturing industries, known as a "near vs. far" analysis. In all cases, a distance of 5 km was taken as the area of proximity ("exposure") to industrial installations:

- 1) in a first phase, we conducted a "near vs. far" analysis to estimate the relative risks (RRs) of towns at ≤ 5 km from cement, lime, plaster, and magnesium oxide manufacturing industries as a whole. The variable, "exposure", was coded as: a) exposed or proximity area ("near"): towns at ≤ 5 km from any cement, lime, plaster, and magnesium oxide manufacturing facility; b) intermediate area: towns at ≤ 5 km from any industrial installation other than cement, lime, plaster, and magnesium oxide manufacturing facilities; and, c) unexposed area ("far"): towns having no (IPPC+E-PRTR)-registered industry within 5 km of their municipal centroid (reference group);
- 2) in a second analysis, we stratified exposed or proximity area of analysis anterior into 5 groups according to the previously defined categories of industrial activity: Group 1, made up of towns at ≤ 5 km from one or more installations belonging to the category "Cement"; Group 2, if the category was "Lime"; Group 3, if the category was "Plaster"; Group 4, if the category was "Magnesium oxide"; and Group 5, made up of towns lying close to two or more installations belonging to different categories of activity ("multiple pollutant categories"). Intermediate and unexposed areas were defined as in the preceding phase; and,
- 3) lastly, in view of that fact that characteristics of the 67 facilities studied vary, we conducted separate "near vs. far" analyses of the individual installations, with the analysis being confined to an area of 50 km surrounding each such installation so as to have a local comparison group.

For all the above analyses, RRs and their 95% credible intervals (95% CrIs) were estimated on the basis of Poisson regression models, using a Bayesian conditional autoregressive model proposed by Besag, York and Mollié (BYM) (Besag et al., 1991), with explanatory variables:

$$O_i \sim \text{Poisson}(\mu_i), \text{ with } \mu_i = E_i \lambda_i$$

$$\log(\lambda_i) = \alpha \text{Expos}_i + \sum_j \beta_j \text{Soc}_{ij} + h_i + b_i \Rightarrow \log(\mu_i) = \log(E_i) + \alpha \text{Expos}_i + \sum_j \beta_j \text{Soc}_{ij} + h_i + b_i$$

$$\text{Soc}_{ij} = ps_i + ill_i + far_i + unem_i + pph_i + inc_i$$

$$i = 1, \dots, 8098 \text{ towns}, \quad j = 1, \dots, 6 \text{ potential confounders}$$

$$h_i \sim \text{Normal}(\theta, \tau_h)$$

$$b_i \sim \text{Car. Normal}(\eta_i, \tau_b)$$

$$\tau_h \sim \text{Gamma}(\alpha, \beta)$$

$$\tau_b \sim \text{Gamma}(\gamma, \delta)$$

with λ_i being the RR in town i , the number of observed deaths in town i for each cancer site (O_i) being the dependent variable, and the number of expected deaths in town i for each cancer site (E_i) being the offset. All estimates for the variable of "exposure" (Expos_i) were adjusted for the following standardized, sociodemographic indicators (Soc_{ij}), chosen as potential confounders directly from the 1991 census for their availability at a municipal level and potential explanatory ability vis-à-vis certain geographic mortality patterns (Lopez-Abente et al., 2006): population size (ps_i) (categorized into three levels: 0-2000 (rural zone), 2000-10000 (semi-urban zone), and ≥ 10000 inhabitants (urban zone)); percentages of illiteracy (ill_i), farmers (far_i) and unemployed ($unem_i$); average persons per household (pph_i); and mean income (inc_i) as measure of income level. The variable of "exposure" and potential confounding covariates were fixed-effects terms in the models.

Finally, to enable the spatial autocorrelation problem to be assessed, this was estimated by applying Moran's I statistic to the Standardized Mortality Ratios (Bivand et al., 2008). The BYM model takes this problem into account, thanks to the inclusion of two random effects components: a spatial term containing municipal contiguities (b_i); and the municipal heterogeneity term (h_i). Integrated

nested Laplace approximations (INLAs) (Rue et al., 2009) were used as a tool for Bayesian inference. For this purpose, we used R-INLA (The R-INLA project, 2015), with the option of “Laplace” estimation of the parameters. A total of 8098 towns were included, and the spatial data on municipal contiguities were obtained by processing the official NSI maps.

3. Results

Table 1 shows the RRs and 95%CrIs for tumors proving to be statistically significant in towns at ≤ 5 km from installations for the production of cement, lime, plaster, and magnesium oxide as a whole, and Moran’s I test for spatial autocorrelation. Overall, excess cancer mortality was present in both sexes (RR=1.04 in men; RR=1.03 in women). Some cancers – such as all cancers combined (men and women) or tumors of the stomach (men and women), bladder (men), and colon-rectum (men) – showed a statistical significant spatial autocorrelation, and it thus seemed appropriate to use the BYM model in order to take it into account. Special mention should be made of the results for tumors of colon-rectum in both sexes (RR=1.07 in men; RR=1.10 in women), and pleura (RR=1.71), peritoneum (RR=1.62), gallbladder (RR=1.21), bladder (RR=1.11) and stomach (RR=1.09) in men in the vicinity of all such installations. The analyses of this table, including the spatial autocorrelation test, were performed separately for each tumor (see Supplementary data, Tables 2 and 3).

Table 2 shows the RRs and 95%CrIs for cancers that yielded statistically significant results in the analysis of risk stratified by category of industrial activity. For all cancers combined, statistically significant result was observed in the surroundings of cement plants (RR=1.05 in men). As regards specific tumors, attention should be drawn to the significant excess risks found for the following: cancer of colon-rectum in men (RR=1.07) and women (RR=1.11) in the vicinity of cement plants; pleural (RR=1.86), peritoneal (RR=1.61), gallbladder (RR=1.27) and bladder (RR=1.14) cancers in men living near cement plants; melanoma (RR=2.34) in men, in the vicinity of plaster installations; and vulvar and vaginal (RR=1.65), renal (RR=1.54) and brain (RR=1.37) cancers in women, in areas

surrounding lime installations. The analyses of this table were performed separately for each tumor (see Supplementary data, Table 4).

Table 3 shows the RRs in the environs of specific installations for the industrial sector under study, which registered statistically significant excess risks in the “near vs. far” analysis and a number of observed deaths ≥ 10 . Some installations displayed high RRs for more than one tumor simultaneously, especially for installation ‘141’ (“cement”), with statistically significant results for 4 tumors, and installations ‘2584’ and ‘3687’ (“cement”), and ‘2344’ (“lime”), with statistically significant results for 3 tumors. It is also noteworthy to note that there are 3 facilities with significant excess risk for all cancers combined: installations for the production of cement ‘296’ (RR=1.08 in the total population), ‘2581’ (RR=1.18 in women) and ‘3037’ (RR=1.42 in men), located in the province of Barcelona.

In order to document the location and characteristics of the facilities, Supplementary data, Figure 1 depicts the geographic distribution of the 67 installations studied according to the different categories of industrial activity, along with their PRTR codes and year of commencement of operations. Supplementary data, Table 5 gives a detailed description of the type of industrial activity undertaken by each installation and the pollutants emitted during the period 2001-2012. In 2009, the 67 installations released 19,362,577 t of toxic substances to air and 27 t to water, including carcinogens such as arsenic (195 kg to air), chromium (530 kg to air) and polycyclic aromatic hydrocarbons (PAHs) (2059 kg to air). More detailed information on emission amounts is provided in Supplementary data, Tables 6 and 7.

4. Discussion

In general, our results suggest that there is a slight increased risk of dying from all cancers combined in the vicinity of Spanish installations for the production of cement, lime, plaster, and magnesium oxide as a whole. On analyzing cancers individually and stratifying the risk by category of

industrial activity, the following associations were found between tumors and residential proximity to certain types of installations: a) “Cement industries”, and tumors of colon-rectum (men and women), and gallbladder, peritoneum, pleura and bladder (men); b) “Lime industries”, and tumors of vulva and vagina, kidney and brain (women); and, c) “Plaster industries”, and melanoma (men).

Recent studies reinforce the hypothesis of an association between residential proximity to certain types of industrial installations and certain tumors (Garcia-Perez et al., 2013; Pascal et al., 2013). As regards installations for the production of cement, lime, plaster, and magnesium oxide, studies have almost exclusively focused on cement clinker (Fano et al., 2004; Rovira et al., 2011a) and asbestos cement plants (Maule et al., 2007; Musti et al., 2009). In our study, asbestos cement plants were not included (there is only 1 installation in the IPPC+E-PRTR 2009 database), since they do not come under IPPC category 3.1.

4.1 Installations for the production of cement

Cement plants have been identified as one of the major sources of hazardous air pollutants' emissions, including metals, dioxins, PAHs, particulate material, benzene, and polychlorinated biphenyls (European Commission, 2010; Schuhmacher et al., 2004; Sidhu et al., 2001). There are some studies that have analyzed exposure to chromium and cadmium from cement installations (Isikli et al., 2003; Isikli et al., 2006). Other question of interest lies in the replacement of fossil fuel with “alternative” fuel, so-called by the cement industry – which consists in reducing the use of petroleum coke, the usual fuel, using instead waste and/or biomass (Global Alliance for Incinerators Alternatives and Ecologistas en Accion, 2013; Thomanetz, 2012) –, due to waste incineration also generates toxic emissions into the environment (European Commission, 2006). Emissions from waste incineration industries arouse social alarm due to health problems that may be generated among their workers and the surrounding populations, and the financial consequences stemming from a possible administrative intervention. In a previous paper, we study cancer mortality in towns near incinerators, using a similar methodology than in this paper, and we found excess risks for all cancers combined

(total population) and tumors of stomach (women), gallbladder (men), lung (men) and pleura (men) (Garcia-Perez et al., 2013).

To the best of our knowledge, very few epidemiologic studies focused on cancer have been conducted on populations living near cement clinker plants (excluding cement asbestos industries): an Italian case-control study found a significantly greater risk of lung cancer among people living near a cement factory (Fano et al., 2004), whereas the results of another Italian study confirmed significant excesses for cancers like the nervous system, leukemia, mesothelioma and peritoneum in a region with the presence of various industries including cement factories (Salerno et al., 2011). Other type of studies, such as health risk assessments, have assessed carcinogenic risks for the population living in the vicinity of cement plants (Rovira et al., 2011a; Schuhmacher et al., 2004).

In our study, one aspect to be borne in mind is that colorectal cancer is the only tumor with statistically significant excess risks in men and women, which might be indicative of a pathway of environmental exposure. In this case, two possible routes of exposure to the pollution released by these installations are considered: direct exposure to pollutants released to air; and indirect exposure, both to pollutants and liquid effluents which are released to water and can then pass into the soil and aquifers, and pollutants which are released to air and then settle on plants. In such cases, the toxins may pass into the trophic chain, affecting the population. Some authors have already shown associations between colorectal cancer and proximity to industrial pollution sources as metal industries (Garcia-Perez et al., 2010), mining (Fernandez-Navarro et al., 2012), food and beverage sector (Lopez-Abente et al., 2012) and chemical plants (Wilkinson et al., 1997). As regards cement plants, a Brazilian study found a significant elevation on colorectal cancer mortality in an industrialized area with cement industries came into operation in the 1960s, among other facilities (Medrado-Faria et al., 2001), and a Korean occupational study suggested a potential association between exposure in the cement industry and an increased risk of rectal cancer (Koh et al., 2013).

On the other hand, in some tumors of our study (e.g., bladder, pleura and gallbladder) the significant excess risks solely affected men, thus being indicative of a possible occupational-exposure

pathway, assuming that worker's residence was homogeneously distributed. One of the most noteworthy results is the high excess risk of pleural and peritoneal cancers in men in the proximity of cement plants. These tumors are related to asbestos and natural fibers exposure (Boffetta and Stayner, 2006) and with respect to industrial pollution sources, Salerno et al. (2011) highlighted excesses for mesothelioma and peritoneal cancer in an industrialized area with the presence of cement industries. An industrial sector related to cement industry is the production of asbestos cement or fiber-cement, which we do not include in our study. Some epidemiologic studies have related residential proximity to asbestos cement plants and increases pleural and peritoneal mesothelioma risks (Maule et al., 2007; Musti et al., 2009), although we have no evidence that cement clinker installations in Spain had manufactured asbestos cement. Other tumors in our study that could be related to occupational exposure are the referred to stomach and bladder: some authors have reported associations between cement dust exposure and stomach (Koh et al., 2011a) and bladder (Smalley et al., 2004) cancers, something that could be related with significant excess risk of these cancers detected only in men in our study.

With respect to specific cement installations, the Spanish "Rovira i Virgili" University assessed carcinogenic risks derived from exposure to metals and dioxins for the population living in the vicinity of some Spanish cement plants and these risks were within the ranges considered as acceptable according to national and international standards. The authors studied the installation '3037' and, although the cancer risks due to dioxins slightly increased, a reduction of the total carcinogenic risks, including metals, was noted (Rovira et al., 2011b; Schuhmacher et al., 2009); in our study, we found statistically significant excess risks in men for all cancers combined and colorectal cancer. Insofar as installation '2582' is concerned, Rovira et al. (2011a) noted that risk values for the population living near the facility were similar to those found for residents living in a number of urban and suburban areas; in our study, we found significant excess risks in tumors of liver in men, and vulva and vagina in women. Finally, Schuhmacher et al. (2004) studied the facility '3036' and the results showed that the incremental individual risk due to emissions of the cement plant was very low in relation to cancer

risks produced by pollutants such as metals and dioxins emitted by the cement kiln; in our study, we found a significant excess risk in breast cancer.

4.2 Installations for the production of lime and plaster

We have found surprising results affecting only in women, with high excess risks in tumors of vulva and vagina, kidney and brain, in the environs of installations for the production of lime. In Spain, women entered the job market comparatively recently, and it is difficult to imagine that occupational exposure would cause excess mortality among women and not among men (e.g., in 1989 the percentage of women working in the Spanish industries for the production of non-metallic minerals was only 11% (National Statistics Institute, 2015)). On the other hand, we have found elevated risks for pleural cancer and melanoma in towns close to installations for the production of plaster.

To the best of our knowledge, no epidemiologic studies have been conducted on populations living near these types of installations. Insofar as occupational exposure is concerned, some studies have reported associations between mineral dust exposure and lung cancer (Bardin-Mikolajczak et al., 2007) and infectious pneumonia (Koh et al., 2011b) among workers at lime and plaster manufacturing facilities.

One of the principal strengths of our study resides in the completeness of its exploratory analysis, which consisted of an in-depth examination of mortality due to 33 types of cancer. Another strength was its use of a methodological approach to perform the statistical analysis, based on a hierarchical spatial model at a municipal level, with inclusion of explanatory variables, in which the use of spatial terms in the model, not only meant that it was less susceptible to the presence of the ecological fallacy (Clayton et al., 1993), but also ensured that the geographic heterogeneity of the distribution of mortality was taken into account. Moreover, the method of estimation afforded by INLA, as an alternative to Markov chain Monte Carlo methods, amounts to a qualitative leap in the use of hierarchical models with explanatory variables (Rue et al., 2009). A consideration to bear in mind is

that spatial models are more restrictive to detect potential statistical associations and robust to possible risk factors not included (residual confounding) than standard Poisson regression models (Garcia-Perez et al., 2013).

Further advantages of the study are: elimination for study purposes of those installations that had come into operation most recently, and whose possible influence on tumor development is debatable if the minimum latency periods of the tumors analyzed is taken into account; and inclusion of towns lying close to industries other than cement, lime, plaster, and magnesium oxide manufacturing facilities, as the "intermediate category" in the analyses, something that avoids the confounding effect of such industries (which release toxic substances that could be related to the tumors under study) and allows for the establishment of a "clean" reference group made up of towns having no industry in their vicinity.

Aside from the limitations inherent to all ecologic studies, in our case mention should also be made of the following: the inclusion of many variables in the models that could make the analyses very susceptible to type I error; the non-inclusion of possible confounding factors that might be associated with distance (though adjustment for socioeconomic variables goes some way to mitigating this lack of information, since many life-style-related risk factors, such as smoking, alcohol consumption, type of diet or infectious agents, show a distribution correlated with socioeconomic status (Prattala et al., 2009; Woitas-Slubowska et al., 2010), due to the tendency of poor communities to live near industrial facilities in urban areas (Parodi et al., 2005)); the use of distance from town of residence to industrial centers as a "proxy" of population exposure to industrial pollution, based on the assumption of an isotropic model, since real exposure may depend on prevailing wind patterns or geographical landforms (though this would limit the capacity for detecting positive results, without invalidating the associations found); and the use of mortality rather than incidence data, due to the absence of a national population-based incidence register (though in Spain, tumors with lower survival rates are well represented by death certificates (Perez-Gomez et al., 2006)).

One exposure that could confound the results is smoking, a recognized risk factor in some tumors studied but for which there is no information at a municipal level. We tried to minimize this problem by carrying out a separate analysis by sex, and adjusting for sociodemographic variables that could, in themselves, define subgroups with different proportions of smokers. Occupational exposures may also have influenced the difference between men and women in our results, something impossible to control for due to lack of data at a municipal level.

Lastly, a critical decision in the definition of “near” category in the “exposure” variable was the choice of radius. We decided to select a 5-kilometer radius around installations, in line with the distance used by other studies (Deziel et al., 2012; Maule et al., 2007) and is justified because, in these types of studied, if some increase in risk were to be found, it would most likely be in zones lying closest to the pollutant source.

5. Conclusion

Our results indicate a possible ecologic association between residential proximity to installations for the production of cement, lime, plaster, and magnesium oxide as a whole and an excess risk of dying from some cancer locations, mainly in tumors of colon-rectum (men and women) and stomach, gallbladder, peritoneum, pleura, and bladder (men).

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