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Burden of disease from breast cancer attributable to smoking and second-hand smoke exposure in Europe

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List of abbreviations:

SHS: second-hand smoke

DALYs: disability-adjusted life years

EU: European Union

IARC: International Agency for Research on Cancer

CalEPA : California Environmental Protection Agency

US: United States

AF: attributable fraction

SIR: smoking impact ratio

RR: Relative Risk

UI: uncertainty interval

GBD: Global Burden of Disease, Injuries and Risk Factors Study

Abstract

Smoking and second-hand smoke (SHS) exposure have been recently linked to a higher risk of breast cancer in women. The aim of this work is to estimate the number of deaths and disability-adjusted life years (DALYs) from breast cancer attributable to these two risk factors in the European Union (EU-28) in 2017.

The comparative risk assessment method was used. Data on prevalence of smoking and SHS exposure were extracted from the Eurobarometer surveys, relative risks from a recent meta-analysis, and data on mortality and DALYs from breast cancer were estimated from the Global Burden of Disease, Injuries and Risk Factors Study.

In 2017, 82,239 DALYs and 3,354 deaths from breast cancer in the EU-28 could have been avoided by removing exposure to these two risk factors (smoking and SHS exposure). The proportion of DALYs from breast cancer lost respectively from smoking and SHS exposure was 2.6% and 1.0%, although geographically distributed with significant heterogeneity.

These results represent the first estimates of breast cancer burden in women attributable to smoking and SHS exposure for the EU-28. It is important to increase awareness among women, health professionals and wider society of the association between smoking, SHS exposure and breast cancer, a relationship that is not widely recognised or discussed.

Keywords: breast cancer; burden of disease; population attributable fraction; second-hand smoke; smoking

Novelty and Impact

In 2017 in the European Union (EU-28) an estimated 82,239 years of life with disability and 3,354 deaths from breast cancer could have been avoided by removing smoking and second-hand smoke exposure.

Among all disability-adjusted life years lost from breast cancer, 2.6% were due to smoking and 1.0% to second-hand smoke exposure.

Although smoking (including SHS exposure) is not considered a major risk factor for breast cancer risk, the burden of disease from breast cancer attributable to smoking and SHS exposure is large in EU-28.

The association between smoking and second-hand smoke exposure with breast cancer is poorly recognised, and it is important to increase awareness among health professionals and the public.

Introduction

Tobacco smoke is the most ubiquitous, preventable human carcinogen and breast cancer is the leading cause of cancer among women, accounting for nearly one in four of all new cancer diagnoses worldwide in 2018, and about 15% of female cancer deaths. Among European women, breast cancer accounted for 523,000 new cases (28% of total cancers) in 2018, being also the leading cause of cancer-related deaths (138,000 deaths, 16% of total female cancer deaths), with the exception of Northern European countries, where it is now preceded by lung cancer[1].

Until 2004, reports published by expert groups, such as the International Agency for Research on Cancer (IARC), California Environmental Protection Agency (CalEPA), or the United States (US) Surgeon General, did not report any association between smoking and breast cancer. The 1986 IARC monograph even indicated that smoking reduced breast cancer risk[2].

The 2005 CalEPA Report for the first time concluded that there was a positive association between smoking and breast cancer risk[3], followed a few years later by a report by a group of Canadian experts[4], and then by the 2012 monograph of the IARC, which for the first time, mentioned a causal relationship[5]. Also, the 2014 US Surgeon General reported an increased risk of breast cancer in smokers, particularly in post-menopausal women[6].

Regarding second-hand smoke (SHS) exposure, both the 2005 CalEPA Report and the Canadian study reported a relationship consistent with causality between SHS exposure and occurrence of breast cancer, particularly in women before menopause, whereas the 2014 US Surgeon General reported a possible association in non-smoking pre-menopausal women[3-4,6].

The 2015 meta-analysis of all published studies on this research topic reported significant 9% and 20% increases in breast cancer risk respectively in smoking women and among non-smoking women exposed to SHS, surprisingly. However, high heterogeneity was observed among studies, and respectively a 10% and 7% risk increase if considering only prospective studies accounting for heterogeneity[7].

Several theories have been put forward to explain why SHS exposure could have a similar or stronger effect on breast cancer than active smoking, and the debate is ongoing. According to one theory, smoking has an association with breast cancer weaker than expected due to the role of being both an anti-estrogenic protective factor and a risk factor for breast cancer[2]. According to others, SHS exposure has a predominant effect in pre-menopausal cancers, a hypothesis strongly supported by a Japanese cohort study that found a three times higher risk of developing breast cancer among SHS exposed women in pre-menopausal age, but not in post-menopausal age[8].

Overall, smoking prevalence in European Union (EU-28) has shown a slight decrease in recent years, yet with heterogeneous trends among countries, and, since the widespread implementation of smoking bans, important reductions in SHS exposure in EU-28 have been observed [9].

It is important to highlight the impact that both smoking and SHS exposure have on women's health and to quantify the numbers of deaths and disability-adjusted life years (DALYs) lost that could be avoided. The aim of this work, conducted within the TackSHS project, is to estimate the number of deaths and DALYs from breast cancer attributable to smoking and SHS exposure in the EU-28 in 2017 [10].

Material and methods

The burden from breast cancer attributable to smoking and SHS exposure was obtained using the comparative risk assessment method [11]. Briefly, the smoking and SHS attributable fraction (*AF*) for each country and age-class was first estimated using Levin's formula

$$AF = \frac{p \cdot (RR - 1)}{p \cdot (RR - 1) + 1},$$

where RR is the relative risk for exposed to smoking or SHS compared to non-exposed.

In the estimation of the *AF* from smoking *p* is the smoking impact ratio (SIR)

$$SIR = \frac{C_{LC} - N_{LC}}{S^*_{LC} - N^*_{LC}} \cdot \frac{N^*_{LC}}{N_{LC}},$$

where C_{LC} and N_{LC} are the age-specific lung cancer mortality rate respectively for the all country under study and for never smokers only, and S^*_{LC} and N^*_{LC} are lung cancer mortality rates for smokers and never-smokers, respectively, in a reference population. The SIR represents the accumulated risk from smoking, using lung cancer mortality excess as a biological marker for accumulated smoking hazards. Since the effect of smoking on breast cancer depend on the smoking exposure history, such as age of starting smoking and number of cigarettes smoked per day, the SIR is usually preferred to the smoking prevalence alone that is an insufficient indicator of accumulated risk from smoking [12].

In the estimation of the *AF* from SHS, *p* is the 10-years lagged age and country-specific prevalence of SHS exposure. A 10-year lag between SHS exposure and breast cancer death/occurrence was assumed in computing the AF, due to an expected long latency, as for active smoking[11].

The number of breast cancer deaths/DALYs attributable to smoking was then obtained by multiplying the age- and country-specific number of breast cancer deaths/DALYs by the corresponding attributable fractions, and the burden attributable to SHS exposure was estimated among non-smoking women, because the impact of smoking could mask the effect due to SHS[11].

The Relative Risks (RR) for smoking women compared to non-smokers was 1.10 (95% confidence interval [95%CI]:1.09-1.12), and the RR for women exposed to SHS compared to non-exposed was 1.07 (95% CI:1.02-1.13)[7]. The sources of data used in the analysis are reported in Table 1.

For each estimate of deaths and DALYs attributable to smoking and SHS exposure, an uncertainty interval (UI) was obtained with a Monte Carlo procedure[11].

A sensitivity analysis was carried out by using RR estimated pooling all prospective and retrospective studies, even if highly heterogeneous (RR for smoking: 1.09 (95% CI:1.06-1.12); RR for SHS exposure 1.20 (95% CI:1.07-1.33)) [7]. Moreover, an analysis estimating the burden form smoking by using the 10-years lagged prevalence of smoking instead of the SIR in the AF estimation was also performed.

Results

In the EU-28 in 2017, the number of DALYs from breast cancer attributable to smoking and SHS exposure was estimated as of 50,610 (UI:42,506-61,471) and 10,123 (UI:6,793-14,377) respectively, and the number of deaths was 2,340 (UI:1,953-2,886) and 379 (UI:239-601). The proportion of breast cancer DALYs attributable to smoking and SHS exposure on the 2,254,992 total DALYs from breast cancer were respectively 2.2% and 0.4% (Figure 1), whereas the proportion of deaths were 2.3% and 0.4%, respectively (101,935 total deaths from breast cancer). In terms of both DALYs and deaths, the highest burden due to both risk factors (smoking and SHS exposure) was estimated in Denmark, Malta, Croatia, Hungary and in the United Kingdom, with a proportion on the total breast cancer DALYs and deaths higher than 4% and 5%, respectively. The lowest burden was estimated in Cyprus, Lithuania, Latvia, Italy and Estonia with a proportion less than 1.5%.The proportion of DALYs and deaths from breast cancer attributable to smoking was higher than that due to SHS exposure for all EU-28 countries (Figure 1).

In the sensitivity analysis using meta-analytical RR of breast cancer with a high heterogeneity, the rank of the countries by the burden from both smoking and SHS exposure was similar to the main results, but for some countries, i.e. Cyprus, Lithuania, Italy, Romania, Slovenia, Spain, and Bulgaria, the proportion of DALYs from breast cancer attributable to SHS exposure was higher than that due to smoking.Using the 10-year lagged smoking prevalence instead of the SIR in the AF estimation produced an estimate of 48,619 (UI:40,067-58,386) and 10,122 (UI:6,791-14,365) DALYs from breast cancer attributable respectively to smoking and SHS exposure, and 1,752 (UI:1,387-2,222) and 378 (UI:239-603) deaths.

Discussion

In 2017, 50,610 (2340) and 10,123 (379) years of life lived with disability (deaths) could have been avoided, by removing respectively smoking and SHS exposure in the home, in the EU-28, and in all countries the burden from smoking was larger than from SHS exposure. The burden from these two risk factors varied considerable across EU-28 countries, with a geographic gradient. On the one

hand, the North-Western countries showed the largest proportion of breast cancer DALYs attributable to smoking. In these countries, as well as in Austria, Czech Republic, Finland, Hungary, Ireland, The Netherlands, Poland, Slovenia, and Sweden, lung cancer was the leading cause of cancer deaths among women, as a consequence of earlier widespread tobacco consumption among women[1]. Moreover, in most of these countries SHS exposure prevalence is lower with consequently lower burden from SHS.

On the other hand, South-Eastern EU-28 countries showed comparatively greater exposure to SHS and thus larger proportions of breast cancer DALYs attributable to SHS exposure, with over 0.7% in Greece, Bulgaria, and Hungary. By considering a higher risk from SHS exposure, even if estimated with a large heterogeneity, the same countries showed proportions of breast cancer DALYs attributable to SHS exposure over 1.6%. In the South-Eastern countries the burden from breast cancer due to smoking was lower than that due to SHS exposure as a consequence of the lower smoking prevalence than that recorded among women of North-Western countries.

Differently from other studies, the analyses on SHS exposure were carried out by considering household exposure only in order to explore the burden unrelated with the current legislation.

The SIR approach in the estimation of the burden attributable to smoking is usually the preferred method because it considers the accumulated risk from smoking, but also because uses lung cancer mortality data, which are easily available for all countries [16]. Using a lagged prevalence of smoking in order to take into account for the time period between exposure and cancer occurrence, gives smaller attributable fractions than SIR-based estimates among females [17], and this is confirmed in our sensitivity analysis.

The GBD framework provides a comprehensive assessment of risk factor exposure and attributable burden of disease, estimated for 2017 in EU-28 a PAF to smoking of 6.8% and 5.7% for DALYs and deaths, respectively [13]. Another study on the burden from smoking on cancers that analysed five European cohorts reported a proportion of attributable DALYs of 4.7%[18], whereas a study carried out in Norway estimated a PAF to smoking of 11.9% [19]. Similar values were estimated in the

present study for northern countries, such as Denmark (5.9%) and Great Britain (4.8%). Possible explanations of such differences could be in the distributions of risk factors and RR in the populations under study.

The association between SHS exposure and breast cancer needs further evidence. Within the last ten years only four groups investigated the burden from breast cancer due to SHS exposure. The results of these studies produced estimates of attributable fractions between 1.07% and 1.68% that are higher in comparison to our estimates[20]. The PAF to SHS exposure estimated from GBD for the EU-28 are 1.7% and 1.4% for DALYs and deaths, respectively, whereas the Norwegian study estimated a PAF of 3.2% [13]. The main differences in these results could be explained by the different definition for SHS exposure, that in our case refers to household exposure only.

This study has some limitations. In the SIR approach, we are using the lung cancer mortality as an indicator of smoking exposure history; however, the relationship of active smoking to breast cancer may depend also from other measures, such as years of smoking before first childbirth[20]. Moreover, in the SIR estimation, as lung cancer death rates in non-smokers of the population under study we used, for all countries, a pooled estimate from never smokers of European Descent extracted from the Thun et al. (2008) study [14] since no rates specific for each Europe Union country was available. We used an estimate of RR of breast cancer for overall SHS exposure, that are extracted from different studies exploring the effect of SHS exposure defined in several different ways, i.e. spousal exposure, household exposure, workplace exposure. This could generate biased conservative estimates since the analyses are carried out by considering household exposure only. Moreover, we assumed the same RR for all ages since there were no robust meta-analytical RR estimates by age in the literature, even if there is evidence that pre-menopausal and post-menopausal breast cancer risks for active and SHS risks may differ[8].

In conclusion, to our knowledge, this is the first estimate on the burden from breast cancer attributable to smoking and SHS exposure in the EU-28. Although smoking (including SHS exposure) is not considered a major risk factor for breast cancer risk, the burden of disease from

breast cancer attributable to smoking and SHS exposure is large in EU-28, and, given that awareness of both smoking and SHS exposure as risk factors for breast cancer is still low among the population, it is important to spread this link among the public and all stakeholders. Smoking and exposure to SHS are modifiable risk factors, and therefore important objects of primary prevention policies, in addition to the current population-based breast cancer early detection programmes across Europe.

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Competing interest: none declared.

Data availability: The data and the code that support the findings of this study are available from the corresponding author upon reasonable request.

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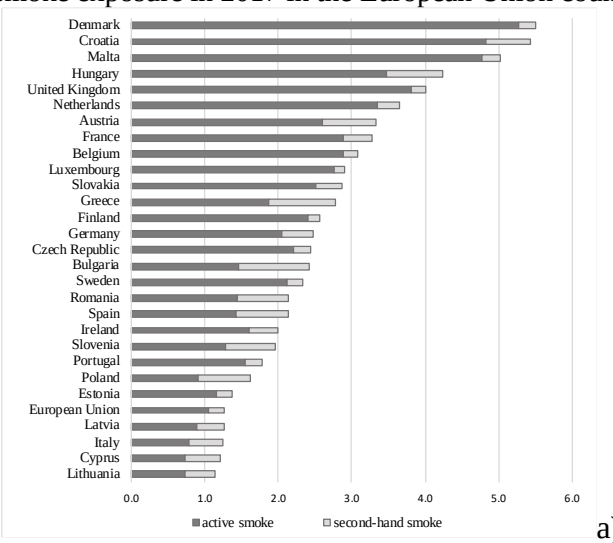
Table 1 – Sources of data used for the analyses. SHS: second-hand smoke.

Variable	Source
Country and age-specific prevalence of SHS exposure at home in non smoking women in 2006 for the estimation of attributable fractions (defined as being ever exposed in the home daily)	Eurobarometer surveys[9]
Country and age-specific prevalence smoking women in 2017 for the estimation of non-smoking women	Eurobarometer surveys[9]
Relative risk of breast cancer for exposed to SHS compared to not exposed and for smokers compared to non smokers	Meta-analysis [7]
Country and age-specific lung cancer mortality rate in 2017 (C_{LC}) for SIR estimation	Global Health Data Exchange of the Global Burden of Disease study [13]
Country and age-specific lung cancer mortality rate for never smokers only (N_{LC})	Pooled estimate among white lifelong never smokers of European Descent [14]
Lung cancer mortality rates for smokers and never-smokers in a reference population (S^*_{LC} , N^*_{LC})	Estimate from Cancer Prevention 2 study [15]
Country-specific estimates of mortality and DALYs from breast cancer	Global Health Data Exchange of the Global Burden of Disease study [13]

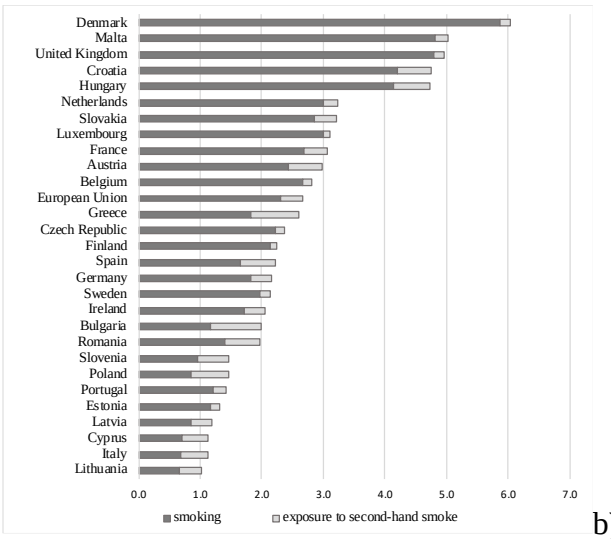
Table 2 – Prevalence of household second-hand smoke exposure in 2006 (SHS), smoking prevalence in 2006 (smoking), Smoking Impact Ratios (SIR), disability adjusted life years from breast cancer in 2017 (DALYs) and deaths from breast cancer in 2017 (deaths) for women aged 15-80+ years with 95% confidence intervals (CI) or uncertainty intervals (UI).

country	SHS % (95% CI)	Smoking % (95% CI)	SIR % (95% UI)	DALYs % (95% UI)	Deaths % (95% UI)
Austria	10.3 (6.5,14.1)	24.3 (19,29.5)	22.7 (15.7,43.6)	35328 (41237,29942)	1688 (1462,1938)
Belgium	4.5 (2.2,6.8)	21.9 (17.4,26.5)	24.5 (16.8,46.8)	52913 (62554,44121)	2450 (2088,2831)
Bulgaria	15 (10.4,19.5)	29.6 (23.9,35.3)	11.2 (7.1,28.2)	34462 (41761,28086)	1356 (1120,1624)
Cyprus	9.3 (3,15.6)	16.1 (10.9,21.2)	5.9 (3.9,19.2)	4645 (5972,3504)	169 (129,212)
Czech Republic	6.2 (3.2,9.2)	23.1 (18.5,27.8)	18.3 (12.9,36.9)	37669 (44246,31704)	1708 (1465,1974)
Germany	6.6 (4,9.2)	25.3 (22.3,28.3)	17.3 (11.8,36)	431661 (529364,347861)	20000 (16469,24073)
Denmark	4.2 (2,6.3)	28.8 (21.8,35.9)	44.7 (31.9,73.4)	27614 (32734,23135)	1294 (1106,1505)
Estonia	3.5 (0.8,6.1)	24 (9.9,38.1)	9.6 (6.6,24.4)	4996 (6370,3831)	219 (172,274)
Spain	10.8 (6.7,14.8)	28.3 (25.9,30.7)	13.1 (9.3,29.3)	151940 (178790,128086)	6749 (5815,7784)
Finland	2.4 (0.6,4.1)	22.5 (16,29)	20.7 (13.5,42.3)	21210 (25316,17655)	917 (777,1073)
France	7.9 (4.6,11.2)	27 (24.8,29.1)	24.8 (17,47)	282360 (334740,235115)	13321 (11376,15442)
United Kingdom	4.2 (1.9,6.5)	31.9 (28.4,35.4)	34.4 (24.5,59.1)	307453 (324528,291743)	13757 (13356,14190)
Greece	12.1 (7.8,16.5)	36.7 (31.4,42)	16.2 (10.8,34.9)	48772 (57738,40731)	2286 (1953,2652)
Croatia	11.4 (7.1,15.6)	25.1 (17.9,32.3)	44.2 (30.1,68)	19720 (23238,16635)	951 (815,1107)
Hungary	14.9 (9.9,19.9)	29.3 (24.3,34.3)	30.3 (21.6,54.4)	45970 (53912,38886)	2045 (1757,2365)
Ireland	8.6 (5.2,11.9)	29.4 (21,37.9)	13.8 (9.4,30.9)	18578 (22549,15134)	746 (617,892)
Italy	7.2 (3.4,10.9)	23.8 (21.8,25.7)	6.7 (4.4,20.4)	271655 (318234,228855)	12769 (10970,14667)
Lithuania	4.6 (1.5,7.8)	20.2 (12.6,27.8)	5.7 (3.6,19.1)	12627 (15128,10414)	524 (439,620)
Luxembourg	2.6 (0,5.5)	23.4 (0.8,45.9)	24.4 (16.8,46.7)	2415 (3046,1862)	104 (82,128)
Latvia	8.9 (4.8,13)	21.3 (10.4,32.2)	7.2 (4.8,21.2)	9098 (11498,7104)	393 (312,491)
Malta	3.2 (0,6.9)	21.6 (-2.1,45.4)	41.3 (28.9,69.8)	2328 (2815,1887)	100 (83,120)
Netherlands	5.6 (2.9,8.3)	27.5 (23.5,31.5)	28.3 (19.8,51.4)	88115 (103121,74613)	3859 (3342,4430)
Poland	13.8 (9.4,18.2)	29.8 (27.2,32.4)	7.5 (4.6,22.3)	148977 (176781,123973)	6189 (5224,7244)
Portugal	4.5 (1.7,7.4)	13.9 (10,17.9)	13.3 (8.7,30.6)	43016 (51561,35325)	1927 (1618,2268)
Romania	11.1 (7.1,15.1)	19.9 (16.9,23)	12.2 (8.2,28.6)	82129 (95804,69693)	3345 (2867,3871)
Sweden	4 (2,5.9)	21.8 (16.9,26.8)	18.4 (12.5,37.6)	39547 (45131,34523)	1787 (1590,1999)
Slovenia	11.1 (7.5,14.8)	21.2 (11.1,31.3)	10.9 (6.8,27.4)	8034 (9720,6567)	384 (322,455)
Slovakia	5.6 (2.7,8.4)	18.8 (12.8,24.9)	22 (15.9,41.7)	21760 (27502,16189)	898 (651,1118)
Europe Union	7.6 (4.3,11.1)	26.4 (25.7,27.1)	19.6 (13.5,39)	2254992 (2645390,1907172)	101935 (87977,117345)

Figure 1 – Proportion of a) DALYs and b) deaths from breast cancer attributable to smoking and second-hand smoke exposure in 2017 in the European Union countries.



a)



b)