Burden of Cancer in a Large Consortium of Prospective Cohorts in Europe


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Burden of cancer in a large consortium of prospective cohorts in Europe


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ABSTRACT

**Background:** Disability-adjusted life years (DALYs) are an indicator of mortality, morbidity and disability. We calculated DALYs for cancer in middle-aged and older adults participating in the CHANCES consortium (Consortium on Health and Ageing Network of Cohorts in Europe and the United States).

**Methods:** A total of 90,199 participants from five European cohorts with 10,455 incident cancers and 4,399 deaths were included in this study. DALYs were calculated as the sum of the years of life lost due to premature mortality (YLLs) and the years lost due to disability (YLDs). Population attributable fractions (PAFs) were also estimated for five cancer risk factors, i.e. smoking, adiposity, physical inactivity, alcohol intake, and type II diabetes.

**Results:** After a median follow-up of 12 years, the total number of DALYs lost from cancer was 34,474 (382 per 1,000 individuals) with a similar distribution by sex. Lung cancer was responsible for the largest number of lost DALYs (22.9%), followed by colorectal (15.3%), prostate (10.2%), and breast cancer (8.7%). Mortality (81.6% of DALYs) predominated over disability. Ever cigarette smoking was the risk factor responsible for the greatest total cancer burden (24.0%; 95% CI=22.2%-26.0%) followed by physical inactivity (4.9%; 95% CI=0.8%-8.1%) and adiposity (1.8%; 95% CI=0.2%-2.8%).

**Conclusions:** DALYs lost from cancer were substantial in this large European sample of middle-aged and older adults. Even if the burden of disease due to cancer is predominantly caused by mortality, some cancers have sizeable consequences for disability. Smoking remained the predominant risk factor for total cancer burden.
INTRODUCTION

Mortality and morbidity are the most widely used indicators to evaluate population health, and cancer is one of the leading causes of morbidity and mortality worldwide (1). However, a growing body of literature proposes the use of summary measures of population health, such as the disability-adjusted life years (DALYs), which reflects both healthy life years lost due to premature death as well as years of life spent with disability from a disease (2). DALYs were introduced by the World Bank in 1993, and have been used since then by the World Health Organization to publish regular updates on the burden of diseases and injuries worldwide. The global average burden of all diseases in 2012 was 388 DALYs per 1,000 individuals, of which about 73% was due to premature death and 27% due to non-fatal health outcomes (3). In high income countries, cancer contributed to 17% of the total DALYs lost, with lung, colorectal, and breast cancer being the three leading cancer causes of lost healthy life years.

The increase in survival rates for many cancer types over recent decades warrants the study of not only cancer incidence and mortality but also of the non-fatal consequences of cancer, such as the decrease in quality of life and the relative disability of cancer patients. However, there have been few attempts to estimate the burden of cancer using data from cohort studies. Therefore, the aims of the current study are to calculate DALYs for cancer, overall and by cancer site, in a large and diverse population of middle-aged and elderly Europeans, and to estimate population attributable fractions for selected cancer risk factors (smoking, adiposity, alcohol, physical inactivity, and type II diabetes) based on the calculated DALYs.

METHODS
Study population

CHANCES (Consortium on Health and Ageing Network of Cohorts in Europe and the United States) is a large collaborative project established in 2010 to investigate determinants of health and disease of an aging population (4). Five CHANCES cohorts in Europe (EPIC-Elderly, ESTHER, NSHDS, MORGAM, PRIME BELFAST and Tromsø Study) have provided data for the current analysis. The total study population comprised 90,199 participants after excluding those with prevalent cancer at recruitment. Detailed information about this consortium, its component studies and their cancer assessment methods can be found in the Supplementary Methods and in prior publications (4-10). All participants provided written informed consent, and approval of the study was obtained from the ethics committees at the participating institutions.

Statistical analysis

Calculation of Disability-adjusted Life Years

To calculate DALYs we used the first incident malignant cancer cases (n=10,455) from the five participating cohorts. We added the years of life lost due to premature mortality (YLL) to the years lost due to disability (YLD) following a published formula and the methodological principles employed in the original Global Burden of Disease study (2). We computed the YLL by multiplying the number of deaths due to cancer by the number of years of expected remaining life at the respective age of death according to the West life table (2). The YLD is computed by multiplying the number of first incident cancers by the duration of cancer and a disability weight that reflects the severity of the phases in the natural history of each cancer. We calculated DALYs overall and separately for each cancer site by sex, age group (five-year
groups) and participating cohort. Age standardized DALYs lost per cancer case were also calculated using the direct method to allow for comparison between sexes and cohorts.

The duration of cancer in the YLD calculation was derived from data for each of the participating cohorts, and from external information used in prior publications (2, 11). Duration of disease was defined as the time interval from the cancer diagnosis until death for those who died from cancer. For cancer patients who died from other causes or that were still alive at the administrative end of the study, duration of disease was defined as the minimum of either five years or the time interval from cancer diagnosis until death from other causes or the administrative end of the study, respectively. Disability weights and their 95% confidence intervals (CIs) were derived from prior national burden of disease studies with the person trade-off method using a scale of 0 to 1 (2, 11, 12), where 1 means death and 0 means absolute health (Supplementary Table 1). DALYs were also calculated in sensitivity analyses using the lower and the upper estimates of the 95% CIs for the disability weights in a best and worst case scenario, respectively. In order to apply these disability weights, duration of cancer was divided in four phases (diagnosis and primary therapy, after primary therapy [follow-up], pre-terminal and terminal) (11-13). Patients who died from cancer underwent a period of disability in all aforementioned disease phases, where the terminal phase was uniformly set to one month and the pre-terminal phase set to three months. The diagnosis and primary therapy phase was set to 12 months or less depending on the total duration of the disease (Supplementary Table 2). Cancer patients that were still alive at the administrative end of the study or those who died from a cause other than cancer underwent a period of disability only in the first two disease phases, where the diagnosis and primary therapy phase was set to 12 months.
or less depending on the total duration of the disease (Supplementary Table 2). The calculation of DALYs traditionally includes two social value functions, an age-weighting function and a 3% discount rate (2), and we performed sensitivity analyses to assess the impact of omitting these functions.

**Calculation of population attributable fractions**

We calculated population attributable fractions (PAFs) for five major cancer risk factors namely smoking, adiposity, physical inactivity, alcohol intake, and type II diabetes. We used the generalized Greenland formula that allows adjustment for confounders and terms for more than two levels of exposure (14). Cox proportional hazard models were performed to calculate hazard ratios and 95% CIs by cohort and also after pooling the data from all cohorts together for the association between the afore-mentioned risk factors and cancer incidence and mortality by cancer site using age as the underlying time scale. Proportionality of hazards was verified using the Schoenfeld residuals. The risk estimates in the pooled analysis were compared to summary random effect meta-analysis estimates calculated using the DerSimonian and Laird method (15). The risk estimates from the pooled analysis for cancer incidence were used in the calculation of PAFs for YLDs, whereas the estimates for cancer mortality were used in the calculation of PAFs for YLLs. Models were stratified for age, sex, and mutually adjusted for the latter five risk factors. To further explore residual confounding due to smoking, models were also run among never smokers. Missing values for the five risk factors were assigned to separate categories, and missing indicators were used in the statistical models. Analyses that excluded participants with missing values for any of these variables gave very similar results and are not presented here. Information on the assessment of the five risk factors is
provided in the **Supplementary Methods**. All statistical analyses were performed using STATA version 12 (College Station, TX), and the PAFs were calculated using the built-in routine punafcc.

**RESULTS**

Overall, 90,199 participants were followed-up for a median of 12 years, of whom 10,455 individuals (1,115 per 100,000 person-years) developed a new cancer and 4,399 (519 per 100,000 person-years) died from cancer (**Table 1**). The mean age at recruitment ranged from 54.3 years in the PRIME study to 63.8 years in EPIC-Elderly, and most cohorts had a similar proportion of men and women except for PRIME and EPIC-Elderly. Mean BMI levels ranged from 26.1 to 27.7 kg/m$^2$ with the highest mean BMI observed in the ESTHER and EPIC-Elderly cohorts.

**Table 2** shows the number and age-standardized incidence rates of cancer cases and deaths by cancer site and cohort. Prostate cancer was the most frequently diagnosed cancer in most cohorts with 2,201 overall cases (552 per 100,000 person-years in men), followed by colorectal, breast, and lung cancer, whereas lung cancer was the leading cause of cancer death in all cohorts with 1,062 total events (120 and 203 per 100,000 person-years overall and only in men, respectively) followed by colorectal, prostate, and pancreatic cancer.

The number of YLLs, YLDs and DALYs are shown in **Figure 1** and in **Supplementary Table 3** for the 21 cancer sites with at least 50 overall cases in the CHANCES. **Supplementary Table 4** shows this in more detail by cohort, sex, and five-year age categories. The total number of DALYs lost from these 21 cancers was 34,474 (382 per 1,000 individuals), and there were a total of 28,114 YLLs and 6,360 YLDs lost. YLLs represented 81.6% of total DALYs. Lung cancer was responsible
for the largest number of DALYs lost (22.9%), followed by colorectal (15.3%), prostate (10.2%), and breast cancer (8.7%). When we excluded the time discounting and the age weighting from the DALYs in a sensitivity analysis, the ranking of cancers based on YLLs, YLDs and DALYs remained the same (Supplementary Table 5). Similar results were also observed when we used the lower and the upper estimates of the 95% CIs for the disability weights (Supplementary Table 6).

After analyzing the two components of DALYs by cancer site, lung cancer accounted for the highest number of YLLs (25.6%), whereas breast cancer was responsible for most YLDs (22.4%) (Figure 1 and Supplementary Table 3). For 17 cancers the YLLs were much larger than the YLDs with a YLL to YLD ratio larger than two. Pancreatic and liver cancers registered an extreme ratio of more than 20, as they have the worst documented survival rates, and had the smallest median duration of cancer and among the largest median disability weights in our study (Supplementary Table 3). Breast and endometrial cancer had the smallest YLL to YLD ratios of 1.1 and 1.4, respectively.

The overall burden of cancer was similar by sex, but large differences were observed for certain cancer sites (Figure 2 and Supplementary Table 4). Neoplasms of lung, bladder, stomach, head and neck, esophagus, melanoma, non-Hodgkin's lymphoma, leukemia and multiple myeloma predominantly affected men. In contrast, thyroid, brain and gallbladder cancer were responsible for a greater burden of disease in women. However, the age-standardized DALYs lost per cancer case were slightly larger in women (Supplementary Table 4). In terms of the age distribution, patients aged 65 to 69 years registered for the highest number of absolute DALYs lost due to cancer, but the age-standardized DALYs lost per cancer case were larger in the younger age groups (Supplementary Table 4).
We also estimated the percent of total DALYs lost due to cancer that is attributable to five major risk factors to evaluate the potential for future health gains by reducing population exposure to these factors. **Supplementary Table 7** shows the hazard ratios and 95% CIs for the association of the risk factors with cancer incidence and mortality by cancer site, cohort, and overall after pooling and also meta-analyzing the data from the five participating cohorts. The hazard ratios from the pooled analyses and the meta-analyses were generally in high agreement with very few exceptions. The observed risk estimates in the pooled analyses were also generally concordant in the direction of the effect with the literature evidence from published meta-analyses (**Supplementary Table 7**). **Table 3** depicts the PAFs for risk factors and cancer sites that showed statistical significance in the pooled analysis. Negative values represent protective associations based on the presented risk factor modeling. Current and former cigarette smoking combined was the risk factor responsible for the greatest cancer burden. Ever smoking could explain 24.0% (95% CI=22.2%-26.0%) of total cancer burden followed by physical inactivity (4.9%; 95% CI=0.8%-8.1%) and adiposity (1.8%; 95% CI=0.2%-2.8%). A larger proportion of total cancer burden due to smoking was observed in men (30.5%; 95% CI=27.5%-34.3%) compared to women (18.6%; 95% CI=16.6%-20.4%). Forty-eight percent (95% CI=46.4%-48.8%) of the lung cancer burden was due to ever smoking, followed by 39.3% (95% CI=34.3%-45.1%) for bladder cancer and 34.2% (95% CI=22.4%-43.1%) for esophageal cancer. Overweight and obesity caused an estimated 28.5% (95% CI=12.7%-41.0%) of the burden for endometrial cancer. Abstaining from vigorous physical activity led to 36.0% (95% CI=20.1%-49.0%) of burden from liver cancer.

**DISCUSSION**
This study provides an estimation of the burden of disease due to cancer in five large prospective European cohorts of the CHANCES consortium. The burden of disease due to cancer was 34,474 DALYs, which translates to an average loss of 38.2% of the healthy life expectancy among the individuals in this study. Mortality predominated over disability, but breast and endometrial cancer had sizeable consequences also for disability. Lung cancer was responsible for the largest number of lost DALYs followed by colorectal, prostate and breast cancer. Smoking remained the predominant risk factor for total cancer burden.

The large figure of 382 DALYs lost due to cancer per 1,000 individuals in the current study suggests that there are still considerable opportunities for improving the health burden related to malignancies in Europe. National policies should be further strengthened to reduce cancer incidence and mortality and to prevent disability. This figure is not consistent with that of 54 DALYs per 1,000 individuals calculated by the World Health Organization for Europe in 2012 or by similar estimates from other national burden of disease studies (3, 16, 17). That is because the current study consisted of middle-aged and older adults and calculated DALYs based on only incident cancer cases, and thus it cannot be representative for the burden of disease due to prevalent and incident cancer across all ages like in previous publications. The use of real-life follow-up in the current study enables the prospective calculation of observed information for cancer incidence, mortality, risk factor and confounding variables compared to aggregate modeled data used in prior publications.

The larger proportion of DALYs lost in the current study was sequentially due to lung, colorectal, prostate and breast cancers. This ranking of the top cancers was concurrent to the WHO Global Burden of Disease estimates for cancer in Europe in 2012 and other national burden of disease studies (3, 13, 17). In addition, the ranking
of cancers based on DALYs was similar to the ranking based on mortality, which is in accordance with prior studies (3, 17).

The mortality component carried more weight than the disability component to the DALY calculations for all cancers, which is again in agreement with prior reports (3, 13, 17-24). However, for several cancers (e.g., breast, endometrial, prostate, melanoma, thyroid and head and neck) more than 25% of the global burden of disease was due to years lost due to disability. This strongly highlights the need to consider the effects of cancer interventions on disability as well as on mortality, as survival rates for many cancer types have been increasing during the last decades in high-income countries and this trend is likely to continue (25).

Cigarette smoking was the predominant risk factor related to DALYs, and was responsible for 24.0% of the total cancer burden followed by 4.9% for physical inactivity, 1.8% for adiposity, 1.1% for type II diabetes and 0.5% for alcohol. This highlights the need to strengthen targeted tobacco control strategies in Europe, which are likely to require not only strong government commitment and fiscal measures but also the involvement of tobacco control advocates from the civil society and non-governmental organizations. The Global Burden of Disease study has derived similar estimates for the role of each exposure using an alternative modeling approach, which relies on published risk estimates of associations and prevalence of exposure. Their PAF estimates for total cancer burden were 29% for smoking, 5% for alcohol, 4% for adiposity, 3% for physical inactivity and 3% for low fruit and vegetable intake, which jointly attributed to 37% of total cancer burden and was similar to estimates observed only for cancer mortality (26). Possible explanations for the small differences observed in PAF estimates include different relative risks for the studied associations and/or different distributions of risk factors in the current study. The observed relative
risks in the current study were concordant in the direction of the effect with the literature evidence from published meta-analyses with very few exceptions (Supplementary Table 7). However, the participants in the current study are healthy volunteers, and include few heavy consumers of alcohol or obese participants, which would explain the smaller PAF estimates observed in the current study for alcohol and adiposity. The current study findings might not be generalizable to other non-European populations.

We estimated the burden of cancer based on DALYs in five large European cohort studies with valid and reliable assessments for cancer incidence, mortality and prospective risk factor information. Potential limitations should be also taken into account in the interpretation of our results. The calculation of DALYs depends on subjective estimates for disability weights for cancer, and our findings should therefore be interpreted with caution. However, a prior study that compared DALYs lost due to breast cancer in six European countries has shown that the choice of disability weights in each country had a small influence, whereas the cross-national variation in the epidemiology of breast cancer was responsible for most of the observed differences in the burden of breast cancer by country (27). To better account for this potential limitation, we used previously published disability weights in the Netherlands (12), because they are used in most other burden of disease studies, they are differentiated by disease stage and are calculated for a country with comparable characteristics for diagnosis and treatment procedures to our study population. When we used the lower and the upper estimates of the 95% CIs for the disability weights to recalculate DALYs in a sensitivity analysis, we received very similar results.

Complete survival data were unavailable from the participating cohorts, because they are still ongoing with many participants being alive at the date of
administrative censoring. Therefore, we estimated the duration of cancer in the case of patients who did not die from their cancer as the minimum of either five years or the time interval from cancer diagnosis until the administrative end of the study. The burden of disease of some neoplasms, mainly those that led to death after the date of administrative censoring and of those that most frequently leave sequelae after their potential cure (e.g., prostate, breast, stomach, esophageal, colorectal cancer) are likely to have been underestimated using this assumption, and therefore represent a minimum estimation of the true burden of disease. However, the 5-year criterion for duration of cancer can be considered conservative among survivors and in line with the methodology of other burden of disease studies (11, 12, 17). The duration of some of the disease phases were also based on expert opinion and were consistently applied in other burden of disease studies (11-13, 17).

The calculation of DALYs included social values, such as the age-weighting function and a discount rate, which may generate another source of uncertainty and heterogeneity in our estimates. The age-weighting function gives more relevance to deaths occurring in young and middle-aged individuals, and the 3% discount rate gives more weight to deaths occurring nearer to the present time (2). Other studies have estimated that the joint influence of these two functions on their results was not crucial (13, 28), which was verified in a sensitivity analysis performed for the current study.

In conclusion, our findings along with evidence from a growing literature suggest that there are considerable opportunities for improving the overall health status of middle-aged and older adults in Europe related to malignancies. Efforts for better cancer prevention, early detection and treatment programs should be strengthened, but they should also target the improvement of quality of life and
palliative care for cancer patients. While smoking remains the predominant risk factor for total cancer burden, physical inactivity and adiposity also have important additional effects.
**Funding:** The research leading to these results has received funding from the European Community’s Seventh Framework Programme (FP7/2007–2013) DG-RESEARCH under Grant Agreement No. HEALTH—F3-2010-242244. The EPIC-Elderly study in Spain was supported by the Regional Governments of Asturias, Andalucia, Basque Country, Navarra and Murcia.

**Note:** The study sponsors had no role in the design of the study, the collection, analysis and interpretation of the data, the writing of the manuscript, and the decision to submit the manuscript for publication.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>EPIC-ELDERLY</th>
<th>ESTHER</th>
<th>NSHDS</th>
<th>TROMSO</th>
<th>PRIME</th>
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<tbody>
<tr>
<td>Cohort size, n</td>
<td>39,140</td>
<td>9,220</td>
<td>29,487</td>
<td>9,633</td>
<td>2,719</td>
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<tr>
<td>Mean follow-up, y</td>
<td>11.6</td>
<td>11.0</td>
<td>12.2</td>
<td>13.4</td>
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<tr>
<td>Incident cancer, n</td>
<td>4,218</td>
<td>1,006</td>
<td>3,257</td>
<td>1,527</td>
<td>447</td>
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<tr>
<td>Death from incident cancer, n</td>
<td>2,016</td>
<td>343</td>
<td>1,064</td>
<td>772</td>
<td>204</td>
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<tr>
<td>Mean age (SD), y</td>
<td>63.8 (3.5)</td>
<td>62.0 (6.6)</td>
<td>55.6 (4.9)</td>
<td>62.7 (9.5)</td>
<td>54.3 (2.9)</td>
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<tr>
<td>Male, %</td>
<td>37.9</td>
<td>45.3</td>
<td>50.7</td>
<td>47.5</td>
<td>100</td>
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<tr>
<td>Mean BMI (SD), kg/m²</td>
<td>27.4 (4.5)</td>
<td>27.7 (4.4)</td>
<td>26.5 (4.6)</td>
<td>26.1 (4.0)</td>
<td>26.2 (3.4)</td>
</tr>
</tbody>
</table>

Smoking status, %

- Never: 49.4, 48.6, 40.5, 33.5, 37.4
- Former: 27.6, 31.9, 25.8, 34.9, 32.4
- Current: 21.8, 16.7, 18.4, 31.5, 29.0
- Unknown: 1.2, 2.8, 15.3, 0.1, 1.2

Current alcohol consumption, %

- 0 g/d: 19.6, 29.4, 6.8, 48.6, 40.0
- ≤10 g/d: 44.2, 40.1, 66.8, 43.5, 12.1
- >10 g/d: 36.0, 20.8, 9.6, 6.8, 47.9
- Unknown: 0.2, 9.7, 16.8, 1.1, 0

Vigorous physical activity, %

- No: 44.2, 57.3, 60.0, 66.2, 88.0
- Yes: 31.9, 42.4, 25.5, 32.6, 12.0
- Unknown: 23.9, 0.3, 14.5, 1.2, 0

Diabetes, %

- No: 90.6, 83.6, NR, 95.9, 97.6
- Yes: 7.0, 10.7, NR, 3.7, 2.4
- Unknown: 2.4, 5.7, NR, 0.4, 0
* Abbreviations: CHANCES, Consortium on Health and Ageing Network of Cohorts in Europe and the United States; EPIC-ELDERLY, European Prospective Investigation into Cancer Nutrition-Elderly; NSHDS, Northern Sweden Health and Disease Study; PRIME, MORGAM PRIME BELFAST study; SD, standard deviation; NR, not reported; g/d, grams/day.
<table>
<thead>
<tr>
<th>Cancer site (ICD10)</th>
<th>EPIC-ELDERLY</th>
<th>ESTHER</th>
<th>NSHDS</th>
<th>TROMSO</th>
<th>PRIME</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head &amp; neck (C0-14, 30-32)</td>
<td>131 (9)</td>
<td>52 (3)</td>
<td>28 (27)</td>
<td>9 (8)</td>
<td>64 (12)</td>
<td>24 (4)</td>
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<tr>
<td>Esophagus (C15)</td>
<td>52 (6)</td>
<td>43 (5)</td>
<td>11 (10)</td>
<td>9 (8)</td>
<td>18 (59)</td>
<td>15 (57)</td>
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<tr>
<td>Stomach (C16)</td>
<td>155 (26)</td>
<td>117 (21)</td>
<td>24 (34)</td>
<td>14 (23)</td>
<td>87 (75)</td>
<td>59 (67)</td>
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<td>Small Intestine (C17)</td>
<td>11 (2)</td>
<td>8 (1)</td>
<td>1 (1)</td>
<td>0</td>
<td>14 (3)</td>
<td>5 (1)</td>
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<td>Colorectal (C18-20)</td>
<td>738 (75)</td>
<td>318 (36)</td>
<td>155 (176)</td>
<td>44 (58)</td>
<td>441 (84)</td>
<td>159 (30)</td>
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<tr>
<td>Liver (C22)</td>
<td>84 (17)</td>
<td>78 (16)</td>
<td>15 (13)</td>
<td>11 (8)</td>
<td>34 (7)</td>
<td>24 (4)</td>
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<td>Gallbladder (C23-24)</td>
<td>57 (9)</td>
<td>40 (8)</td>
<td>18 (17)</td>
<td>11 (10)</td>
<td>30 (6)</td>
<td>24 (5)</td>
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<tr>
<td>Pancreas (C25)</td>
<td>173 (25)</td>
<td>155 (22)</td>
<td>35 (30)</td>
<td>32 (23)</td>
<td>77 (14)</td>
<td>70 (12)</td>
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<td>Lung (C34)</td>
<td>639 (80)</td>
<td>539 (70)</td>
<td>128 (125)</td>
<td>100 (88)</td>
<td>186 (36)</td>
<td>144 (26)</td>
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<td>Thymus (C37)</td>
<td>4 (0.5)</td>
<td>2 (0.1)</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (0.4)</td>
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<tr>
<td>Heart (C38)</td>
<td>13 (1)</td>
<td>12 (1)</td>
<td>0</td>
<td>0</td>
<td>8 (1)</td>
<td>6 (0.9)</td>
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<tr>
<td>Bone (C40-41)</td>
<td>7 (1)</td>
<td>5 (1)</td>
<td>1 (0.7)</td>
<td>0</td>
<td>3 (0.5)</td>
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<td>Melanoma (C43)</td>
<td>2 (0.7)</td>
<td>1 (0.5)</td>
<td>23 (20)</td>
<td>4 (3)</td>
<td>92 (17)</td>
<td>15 (3)</td>
</tr>
<tr>
<td>Breast (C50)</td>
<td>763 (98)</td>
<td>130 (18)</td>
<td>159 (282)</td>
<td>17 (24)</td>
<td>488 (175)</td>
<td>65 (22)</td>
</tr>
<tr>
<td>Cervix Uteri (C53)</td>
<td>28 (4)</td>
<td>11 (2)</td>
<td>2 (3)</td>
<td>0</td>
<td>13 (6)</td>
<td>5 (2)</td>
</tr>
<tr>
<td>Corpus Uteri (C54)</td>
<td>152 (15)</td>
<td>28 (3)</td>
<td>27 (44)</td>
<td>3 (5)</td>
<td>130 (45)</td>
<td>18 (6)</td>
</tr>
<tr>
<td>Ovaries (C56)</td>
<td>122 (65)</td>
<td>91 (60)</td>
<td>13 (21)</td>
<td>9 (12)</td>
<td>52 (19)</td>
<td>30 (11)</td>
</tr>
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<td>Prostate (C61)</td>
<td>678 (162)</td>
<td>161 (57)</td>
<td>198 (379)</td>
<td>12 (19)</td>
<td>920 (367)</td>
<td>177 (69)</td>
</tr>
<tr>
<td>Kidney (C64)</td>
<td>114 (13)</td>
<td>59 (9)</td>
<td>41 (35)</td>
<td>10 (7)</td>
<td>82 (16)</td>
<td>35 (6)</td>
</tr>
<tr>
<td>Bladder (C67)</td>
<td>167 (21)</td>
<td>64 (11)</td>
<td>34 (56)</td>
<td>14 (23)</td>
<td>152 (145)</td>
<td>31 (6)</td>
</tr>
<tr>
<td>Brain &amp; CNS (C70-72)</td>
<td>92 (11)</td>
<td>82 (9)</td>
<td>19 (16)</td>
<td>16 (11)</td>
<td>105 (19)</td>
<td>47 (9)</td>
</tr>
<tr>
<td>Thyroid (C73)</td>
<td>17 (1)</td>
<td>2 (0.1)</td>
<td>4 (3)</td>
<td>0</td>
<td>21 (4)</td>
<td>5 (0.8)</td>
</tr>
<tr>
<td>Hodgkin's (C81)</td>
<td>0</td>
<td>0</td>
<td>4 (5)</td>
<td>1 (1)</td>
<td>2 (0.3)</td>
<td>2 (0.3)</td>
</tr>
<tr>
<td>NHL (C82-85)</td>
<td>3 (0.6)</td>
<td>3 (0.6)</td>
<td>29 (25)</td>
<td>10 (7)</td>
<td>110 (20)</td>
<td>43 (7)</td>
</tr>
<tr>
<td>Mul. Myeloma (C90)</td>
<td>3 (0.4)</td>
<td>2 (0.2)</td>
<td>14 (26)</td>
<td>8 (19)</td>
<td>55 (10)</td>
<td>28 (5)</td>
</tr>
<tr>
<td>Leukemia (C91-95)</td>
<td>13 (1)</td>
<td>13 (1)</td>
<td>21 (20)</td>
<td>9 (8)</td>
<td>71 (14)</td>
<td>30 (5)</td>
</tr>
<tr>
<td>Total</td>
<td>4,218</td>
<td>2,016</td>
<td>1,006</td>
<td>343</td>
<td>3,257</td>
<td>1,064</td>
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</tbody>
</table>
### Table 3. Percent of total DALYs* attributable to major cancer risk factors by cancer site in the CHANCES consortium of middle-aged and older adults

<table>
<thead>
<tr>
<th>Cancer site</th>
<th>Smoking (current vs. never)</th>
<th>Smoking (former vs. never)</th>
<th>Current alcohol consumption (&gt;10 vs. 0 g/d)</th>
<th>BMI (≥30 vs. &lt;25 kg/m²)</th>
<th>BMI (25-30 vs. &lt;25 kg/m²)</th>
<th>Vigorous activity (no vs. yes)</th>
<th>Diabetes (yes vs. no)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head &amp; Neck</td>
<td>16.0 (13.0, 18.7)</td>
<td>3.4 (1.2, 5.2)</td>
<td></td>
<td></td>
<td></td>
<td>4.9 (0.6, 8.9)</td>
<td></td>
</tr>
<tr>
<td>Esophagus</td>
<td>17.0 (13.1, 20.0)</td>
<td>14.3 (5.4, 23.1)</td>
<td>14.1 (6.2, 21.9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>6.9 (2.9, 11.8)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colorectal</td>
<td>7.6 (4.8, 10.4)</td>
<td>6.2 (2.4, 10.8)</td>
<td>5.4 (1.8, 8.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver</td>
<td>13.0 (9.0, 17.0)</td>
<td>11.0 (2.1, 19.0)</td>
<td></td>
<td></td>
<td></td>
<td>36.0 (20.1, 49.0)</td>
<td></td>
</tr>
<tr>
<td>Gallbladder</td>
<td>0.7 (0.3, 1.1)</td>
<td></td>
<td>10.0 (3.1, 16.9)</td>
<td>1.1 (0.2, 1.8)</td>
<td></td>
<td></td>
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<tr>
<td>Pancreas</td>
<td>10.0 (6.0, 14.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.0 (0.7, 4.0)</td>
</tr>
<tr>
<td>Lung</td>
<td>21.5 (21.1, 21.9)</td>
<td>24.0 (22.1, 25.0)</td>
<td></td>
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<td>1.8 (0.3, 2.7)</td>
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<tr>
<td>Melanoma</td>
<td>-12.3 (-18.8, -3.6)</td>
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<td>-20.0 (-28.3, -10.1)</td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>4.7 (2.6, 6.3)</td>
<td>5.1 (1.5, 9.1)</td>
<td>2.8 (2.4, 3.8)</td>
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<td></td>
<td></td>
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<tr>
<td>Cervix Uteri</td>
<td>2.1 (1.4, 3.0)</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Corpus Uteri</td>
<td>-11.7 (-18.4, -2.9)</td>
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<td></td>
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<tr>
<td>Prostate</td>
<td>6.5 (3.9, 9.1)</td>
<td></td>
<td>-4.1 (-5.9, -0.7)</td>
<td></td>
<td></td>
<td>-12.1 (-17.3, -5.5)</td>
<td></td>
</tr>
<tr>
<td>Kidney</td>
<td>16.0 (12.0, 19.1)</td>
<td>13.4 (4.6, 21.1)</td>
<td>9.6 (4.7, 14.5)</td>
<td></td>
<td></td>
<td></td>
<td>2.6 (0.9, 4.3)</td>
</tr>
<tr>
<td>Bladder</td>
<td>18.2 (16.2, 20.2)</td>
<td>20.8 (16.0, 24.5)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-6.2 (-9.1, -2.9)</td>
<td></td>
</tr>
<tr>
<td>NHL</td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
<td></td>
<td>-6.5 (-9.6, -2.2)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
* Cox proportional hazard models were performed to calculate hazard ratios and 95% confidence intervals for the association between the afore-mentioned risk factors and cancer incidence and mortality by cancer site after pooling together the data from the five participating cohorts (Supplementary Table 7). PAFs only for the statistically significant risk factor and cancer site incidence or mortality pairs are presented here. Negative values represent protective associations based on the initial risk factor modeling, which were then reversed in this table keeping the negative value to denote the change in the reference groups. Abbreviations: CHANCES, Consortium on Health and Ageing Network of Cohorts in Europe and the United States; BMI, body mass index; NHL, non Hodgkin's lymphoma.

Figure legends

**Figure 1.** Disability-adjusted life years by cancer site in the CHANCES consortium of middle-aged and older adults. [Abbreviations: YLD, years of life lost due to disability; YLL, years of life lost due to premature mortality; DALY, disability-adjusted life years; CNS, central nervous system; NHL, non Hodgkin's lymphoma.]

**Figure 2.** Disability-adjusted life years by cancer site and sex in the CHANCES consortium of middle-aged and older adults. [Abbreviations: YLD, years of life lost due
to disability; YLL, years of life lost due to premature mortality; DALY, disability-adjusted life years; CNS, central nervous system; NHL, non Hodgkin's lymphoma.

References