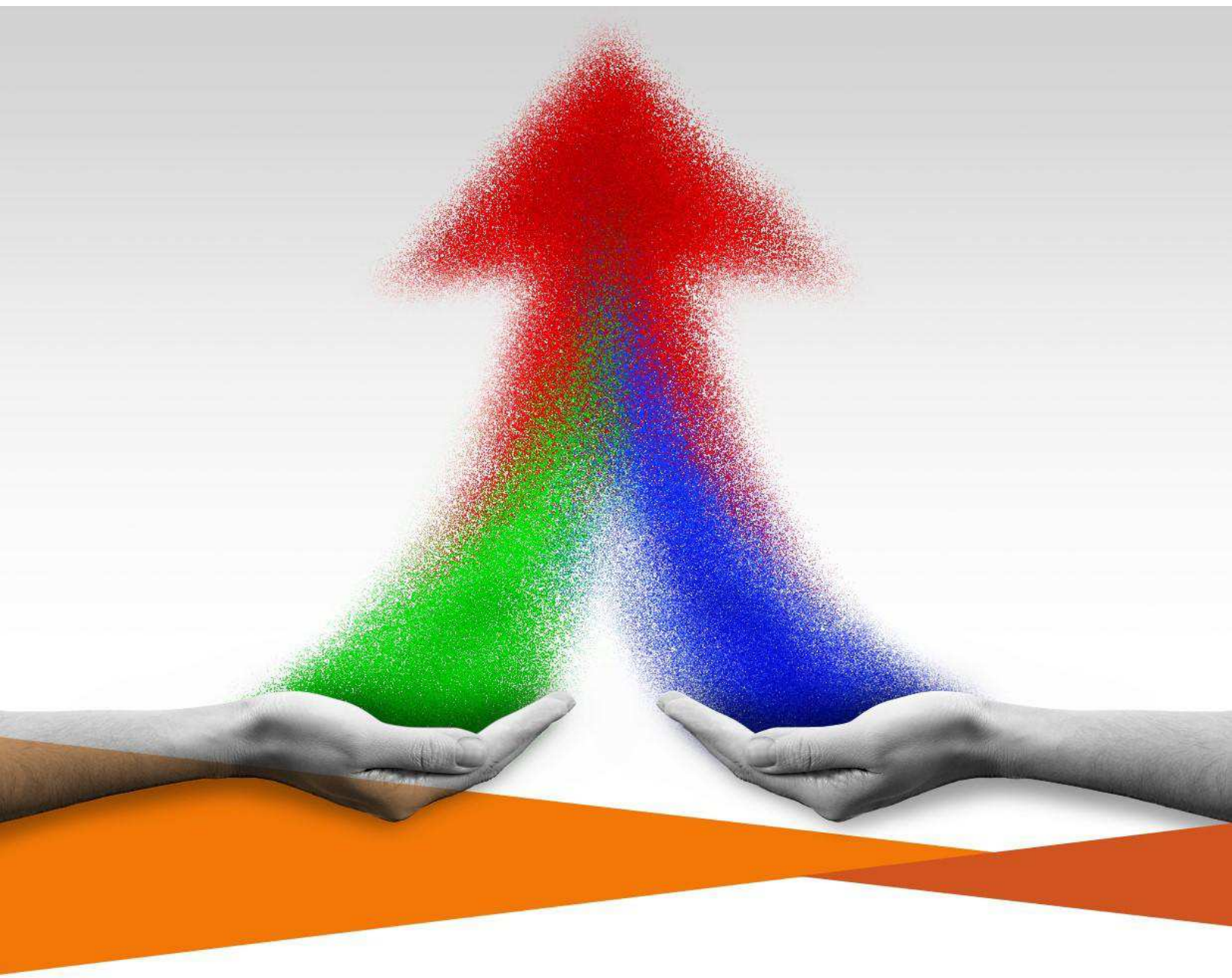

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A novel method for identifying settings for well-motivated ecologic studies of cancer

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A low within-country variability and a large between-country variability in cancer incidence may indicate that ecologic factors are involved in the etiology of the disease. The aim of this study is to explore the within- and between-country variability of cancer incidence to motivate high-quality ecologic studies. We extracted age-standardized incidence rate estimates (world standard population) from 135 regions for the ten most frequent invasive cancers in Europe for non-Hispanic white populations from *Cancer Incidence in Five Continents, Volume X*. We fitted weighted multilevel Poisson regression models with random country effects for each cancer and sex. We estimated intraclass correlation coefficients (ICCs) and 95% confidence intervals (95% CIs). A high ICC indicates a low within- and a high between-country variability of rates. The two cancer sites with the highest ICC among men were prostate cancer (0.96, 95% CI: 0.92–0.99) and skin melanoma (0.78, 0.64–0.93). Among women, high ICCs were observed for lung cancer (0.84, 0.73–0.95) and breast cancer (0.80, 0.69–0.91). The two most prominent sex differences for ICC occurred for cancers of the head and neck (men: 0.70, 0.55–0.85, women: 0.19, 0.08–0.30) and breast cancer (men: 0.04, 0.01–0.07, women: 0.80, 0.69–0.91). ICCs were relatively low for pancreatic cancer (men: 0.23, 0.10–0.35; women: 0.13, 0.04–0.21) and leukemia (men: 0.12, 0.04–0.21; women: 0.08, 0.02–0.14). For cancers with high ICC for which systematic factors of the health care system, screening and diagnostic activities are not plausible explanations for between-country variations in incidence, cross-country sex-specific ecologic studies may be especially promising.

In a review, Diez Roux noted that a low within-country variability and a large between-country variability in the incidence of a disease suggest that factors beyond individuals, referred to as group-level, ecologic, macrolevel or population-level factors, may be involved in the etiology of the disease. Ecologic factors are invariant within a population and, hence, cannot be easily investigated in studies restricted to comparisons of individuals within a population. Diez Roux further stated that "to detect these factors, researchers need studies that compare different populations (or groups) and investigate population-level (or group-level) factors."[1]

In contrast to studies on individuals, the unit of observation in ecologic studies is the population. If the exposure varies little within a population of a country, individual-level studies within the country are inefficient. An ecologic study that includes several countries might be able to achieve substantial variation in mean exposure across populations. Ecologic studies are considered to be hypothesis generating studies that are prone to special biases (*e.g.*, ecologic fallacy) and that frequently suffer from the inability to control for confounding.[2]

Many descriptive studies have focused on comparisons of incidence rates and the substantial international variability of cancer between countries (*e.g.*, Ref. 3). The comparison of the variability of population-based cancer incidence rates within-countries as well as between-countries is rarely undertaken despite the fact that high levels of between-country

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What's new?

For many cancer types, variations in incidence are larger between countries than they are within countries. Such differences suggest that population-level, or ecologic, factors significantly influence the incidence of certain malignancies. Here, incidence rate estimates for 10 invasive cancers were compared across 135 non-Hispanic white populations in countries in Europe and North America. Cancers with high intraclass correlation (ICC) values, indicating low within-country and high between-country variation, included prostate cancer and skin melanoma. Sex-specific variations in ICC were also identified. The methodology employed here could form the basis for in-depth analyses of geographical variations in cancer incidence.

variability and correspondingly low levels of within-country variability may motivate cross-country ecologic studies.

A literature search did not find any cancer-related study that compared the within-country variability with the between-country variability in cancer incidences. Therefore, the aim of this study is to systematically assess the within- and between-country variability of the age-standardized incidence rates (ASRs) of the ten most frequent incident cancers among non-Hispanic white men and women in Europe in 2012 and to motivate high-quality ecologic studies.

Material and Methods

We extracted population-based cancer registry incidence data from *Cancer Incidence in Five Continents, Volume X*[4] (CI5, http://ci5.iarc.fr, accessed on November 5, 2014) and the NORDCAN database (http://www-dep.iarc.fr/NORDCAN/english/frame.asp, accessed on November 5, 2014) alongside the estimated ASRs using the world standard population[5] and the corresponding standard errors. Among the 448 eligible registries, a number of datasets were excluded: (*i*) cancer registries marked with an asterisk, for which there are specific concerns with regard to data quality ($n = 113$ registries or regions, 25.2%), (*ii*) nationwide or pooled estimates, if regional estimates were available ($n = 19$ estimates, 4.2%); (*iii*) cancer registries with multiple ethnicities ($n = 39$, 8.7%) and (*iv*) regional registries within US states ($n = 4$, 0.9%). We did however include the Swedish Cancer Registry, flagged in CI5, given the availability of national and regional estimates and longstanding levels of completeness, as in the other Nordic countries.

We classified each registry estimate by ethnicity. For several US states, rates were reported for "whites" without a distinction between "non-Hispanic whites" and "Hispanics." Some US states reported only rates for the entire state. We therefore examined the proportion of Hispanics, African American and non-Hispanic whites reported in the US census of 2010 (www.census.gov/2010census/, accessed on March 11, 2015). Rates reported for "whites" were classified as "non-Hispanic whites" if the proportion of Hispanics in that US state was <10%. If this proportion was 10% or more, these states were excluded. Rates reported for the whole state were classified as "non-Hispanic whites" if the proportion of Hispanics plus the proportion of blacks in that state was <10%. With the exception of non-Hispanic whites (135 populations), the number of populations with other ethnicities were too few for meaningful analysis. The list of registries that were finally included for the analysis among non-Hispanic white populations is presented in Supporting Information Table 1; all populations were either European or North American.

We confined analyses to the ten most frequent invasive cancers for each sex in terms of ASRs in Europe, as projected for the year 2012[6]: head and neck cancer [International Classification of Diseases, 10th edition ICD-10 (7): C00-C14, C30-C32], stomach cancer (C16), colorectal and anal cancer (C18-C21), pancreas cancer (C25), lung cancer (C33-C34), melanoma of the skin (C43), breast cancer (C50), cervical cancer (C53), uterine cancer (C54), ovarian cancer (C56), prostate cancer (C61), kidney cancer (C64), bladder cancer (C67), thyroid cancer (C73), non-Hodgkin lymphoma (C82-C85, C96) and leukemia (C91-C95). For cancers among the ten most frequent sex-specific tumors that occur among both men and women, we consequently analyzed data for both sexes, although several cancers were not among the ten most common in each of the sexes (*e.g.*, breast cancer among men). Details about the data sources are provided in the Supporting Information.

Statistical methods

To measure the correlation of ASRs within countries, we fitted weighted multilevel Poisson regression models with a random country effect for each cancer and sex separately. These models assume the respective ASRs to be conditionally (on the random country effect) Poisson-distributed. The model equation for a given cancer and sex is:

$$\ln\left(E\left(\mathrm{ASR}_{ij}|u_i\right)\right) = b_0 + u_i,$$

with ASR_{ij} being the age-standardized incidence rate from each region j (=1, ..., n_i) in country i (=1, ..., n), b_0 the overall mean ln(ASR), u_i the random country effect, assumed to be normally distributed with expectation 0 and variance σ^2 [$u_i \sim N(0,\sigma^2)$], ln as the natural logarithm and E denoting the expected value. The parameters estimated are b_0 and the random effects variance σ^2. To account for different precisions in the ASRs, these were weighted with the inverse of the squared standard error.

Table 1. Distribution of age-standardized regional cancer estimates among non-Hispanic whites of the years 2003–2007

			Age-standardized incidence rates per 100,000 person-years among males			Age-standardized incidence rates per 100,000 person-years among females		
Tumor site	ICD-10	Number of estimates	Minimum	Maximum	Weighted mean	Minimum	Maximum	Weighted mean
Head and neck cancer	C00-C14, C30-C32	119	7.9	33.2	16.3	2.1	7.3	4.3
Stomach cancer	C16	135	4.0	29.0	8.2	1.6	13.0	3.8
Colorectal and anal cancer	C18-C21	135	21.8	59.6	36.7	16.7	39.8	24.7
Pancreas cancer	C25	135	4.5	13.7	7.9	2.6	8.6	5.4
Lung cancer	C33-C34	135	16.8	73.6	46.2	5.8	47.6	14.4
Melanoma of the skin	C43	135	2.3	25.6	8.2	2.5	23.4	7.7
Breast cancer	C50	135	0.2	1.4	0.6	35.0	102.1	67.5
Cervical cancer	C53	135				2.0	20.8	7.3
Uterine cancer	C54	135				7.7	23.7	14.7
Ovarian cancer	C56	119				5.8	14.2	10.2
Prostate cancer	C61	135	18.1	141.6	51.1			
Kidney cancer	C64	135	4.8	22.1	10.6	2.1	9.9	5.4
Bladder cancer	C67	119	9.6	48.5	19.1	0.7	8.4	4.0
Thyroid cancer	C73	135	0.8	9.8	2.0	2.3	31.8	6.2
Non-Hodgkin lymphoma	C82-C85, C96	135	4.0	17.4	9.5	2.4	12.7	6.3
Leukemia	C91-C95	135	5.9	17.1	9.7	4.5	9.3	6.3

Mean age-standardized incidence rates are weighted by the inverse of the squared standard error.

Correlations of weighted ASRs within countries are given as intraclass correlation coefficients (ICCs) that we label "intracountry" correlations for convenience. These can be estimated following Stryhn *et al.*[7] and Carrasco[8] *via*

$$\mathrm{ICC} = \left[\exp\left(2b_0 + 2\sigma^2\right) - \exp\left(2b_0 + \sigma^2\right)\right] / \left[\exp\left(2b_0 + 2\sigma^2\right) - \exp\left(2b_0 + \sigma^2\right) + \exp\left(b_0 + \sigma^2/2\right)\right].$$

by inserting the estimated values of b_0 and σ^2. An ICC can be interpreted like a standard Pearson correlation coefficient with a value of 0 suggesting no intracountry correlation (*i.e.*, ASRs from all registries varying randomly across countries) and a value of 1 when all ASRs from single countries would be identical. The higher the ICC, the lower the within-country variability and the higher the between-country variability. It is important to note that the ICC is estimated only from b_0 and σ^2, but does not explicitly use the information from the observed correlations of registries within countries. As a consequence, countries with only one registry also contribute to the estimation of the ICC (because they contribute to the estimation of b_0 and $\sigma 2$) and should not be removed from analysis. As an additional aid to interpretation it should be noted that the ICC is of the form ICC = Var2/(Var2- + Var1) with Var2 ($=\exp(2b_0 + 2\sigma^2) - \exp(2b_0 + \sigma^2)$) denoting the variance at the country level (between-country variance) and Var1 ($=\exp(b_0 + \sigma^2/2)$) denoting the variance at the registry level (within-country variance). As such, an ICC of 0.5 denotes equal variances between and within countries, and ICC > 0.5 points to a between-country variance being larger than the within-country variance. The models were estimated with SAS PROC NLMIXED (SAS, Cary, NC), 95% confidence intervals for ICCs were computed by the delta method.

In a sensitivity analyses, we excluded all countries ($n = 17$ for head and neck cancer, bladder cancer and ovarian cancer and $n = 13$ for all other cancers studied) that provided only a single cancer incidence estimate and re-ran all regression models including 118 or 122 rate estimates, respectively.

Results

The highest weighted means of ASRs across 135 regional rate estimates were observed for prostate cancer (51.1 per 100,000) and lung cancer (46.2 per 100,000) among non-Hispanic white men and breast cancer (67.5 per 100,000) and colorectal cancer (24.7 per 100,000) among non-Hispanic white women (Table 1).

The patterns of variability within- and between-countries, as measured by the ICC, differed by cancer and sex. The four cancer sites with the highest ICC among men included prostate cancer (0.96, 95% CI: 0.92–0.99), melanoma of the skin

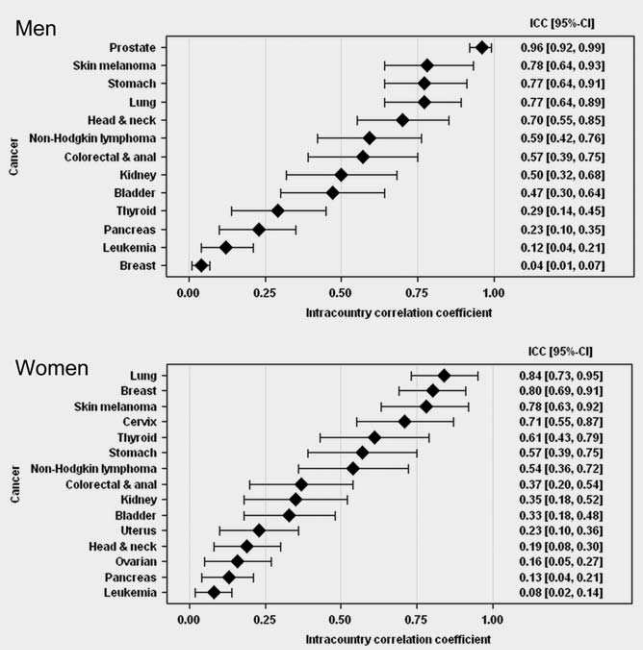

Figure 1. Estimated intracountry correlation coefficients (95% confidence intervals) from a weighted Poisson regression model with a random country effect from age-standardized regional cancer estimates among non-Hispanic white males and females of the years 2003–2007.

(0.78, 0.64–0.93), stomach cancer (0.77, 0.64–0.91) and lung cancer (0.77, 0.64–0.89). Among women, lung cancer (0.84, 0.73–0.95), breast cancer (0.80, 0.69–0.91), melanoma of the skin (0.78, 0.63–0.92) and cervical cancer (0.71, 0.55–0.87) had the highest ICC. The two most prominent sex differences for ICC occurred for cancers of the head and neck (men: 0.70, 0.55–0.85, women: 0.19, 0.08–0.30) and breast cancer (men: 0.04, 0.01–0.07, women: 0.80, 0.69–0.91). ICCs were very low for pancreatic cancer (men: 0.23, 0.10–0.35; women: 0.13, 0.04–0.21) and leukemia (men: 0.12, 0.04–0.21; women: 0.08, 0.02–0.14) (Fig. 1).

Figure 2 displays the variability of ASRs by sex and countries for cancers with a high ICC (men: prostate, women: lung) and a low ICC (men: pancreas, women: leukemia), by sex. The larger the area of the circles, the higher the precision of the rate estimates, that is, the lower the standard error of the rate estimates (Fig. 2). Figures for each cancer site and sex are presented as Supporting Information Figure 1.

The distribution of ICCs tended to shift to lower values after exclusion of 13 or 17 countries (for cancers of the head and neck, ovarian cancer and bladder cancer) for which only a single rate estimate was available, but for other sites, the changes were minor (Supporting Information Fig. 2).

Discussion

To the best of our knowledge, this study is the first to compare the variability of cancer incidence rates both between- and within-countries using weighted multilevel Poisson regression. Our methodological approach may serve as a blueprint for further more in-depth cross-country studies assessing the variability of cancer incidence, for example, by stratification on age, sex and histology. Among the ten most frequent cancers, we observed ICC values ranging from below 0.10 to above 0.90, therefore spanning the whole range of high within-country but low between-country variation (low ICC), through to low within-country but high between-country variations (high ICC), respectively.

Factors related to the health care system can have an impact on the magnitude of the ICCs; they may be high for specific cancers due to the extent of early detection practices or diagnostic enquiry in a population, for example, according to the availability and access to mammography screening programs (*e.g.*, breast cancer) and highly sensitive imaging modalities capable of detecting microinvasive carcinomas (*e.g.*, thyroid cancer).[9] Varying definitions and coding practices of incident cancers between countries and national inconsistencies in certification of death that influence the death certificate only proportion (DCO) of cancer incidence may also have influenced the ICCs.[10] However, factors related to the health care system can also result in low ICCs. For example, nonorganized screening examinations that are not covered by health insurance companies (out-of-pocket screening examinations) depend on the availability of physicians and social and economic factors that affect the willingness to privately pay for out-of-pocket services.

For some cancers, it was expected *a priori* that ICC would be high given the heterogeneity of screening and diagnostic testing activities between countries, but likely homogeneity within countries.[11] The very high ICC for prostate cancer most likely reflects differences in PSA testing (and the attitudes of urologists and GPs to PSA as a diagnostic tool) between countries.[12,13] Breast and cervical cancer, both cancers for which incidence is also influenced by screening activities (mammographic and cytologic screening, respectively), also had high ICCs. Differences may however be due to other factors, and as such, ecological studies may still be potentially fruitful for cancers with large ICCs. As an example, the approach may provide further insights into the etiology of screen-detectable cancers outside the screening ages and of less common cancers or cancers that may vary by subtype.

One may also expect high ICC values if carcinogens are distributed quite homogeneously within countries, but heterogeneously between countries. Smoking might be such a factor. For example, according to the OECD, the prevalence of current smokers among men in 2008 was 34% in Poland and 12% in Sweden (http://ec.europa.eu/health/reports/docs/health_glance_en.pdf, accessed on March 13, 2015). In Germany, the largest country within the EU in terms of population size, the age-standardized prevalence of smoking at the federal state level in 2009 ranged between 23% (Federal State of Baden-Württemberg) and 32% (Federal State of Mecklenburg-Vorpommern).[14] For several cancers where the etiology and the effect of screening on the incidence of cancer is well-

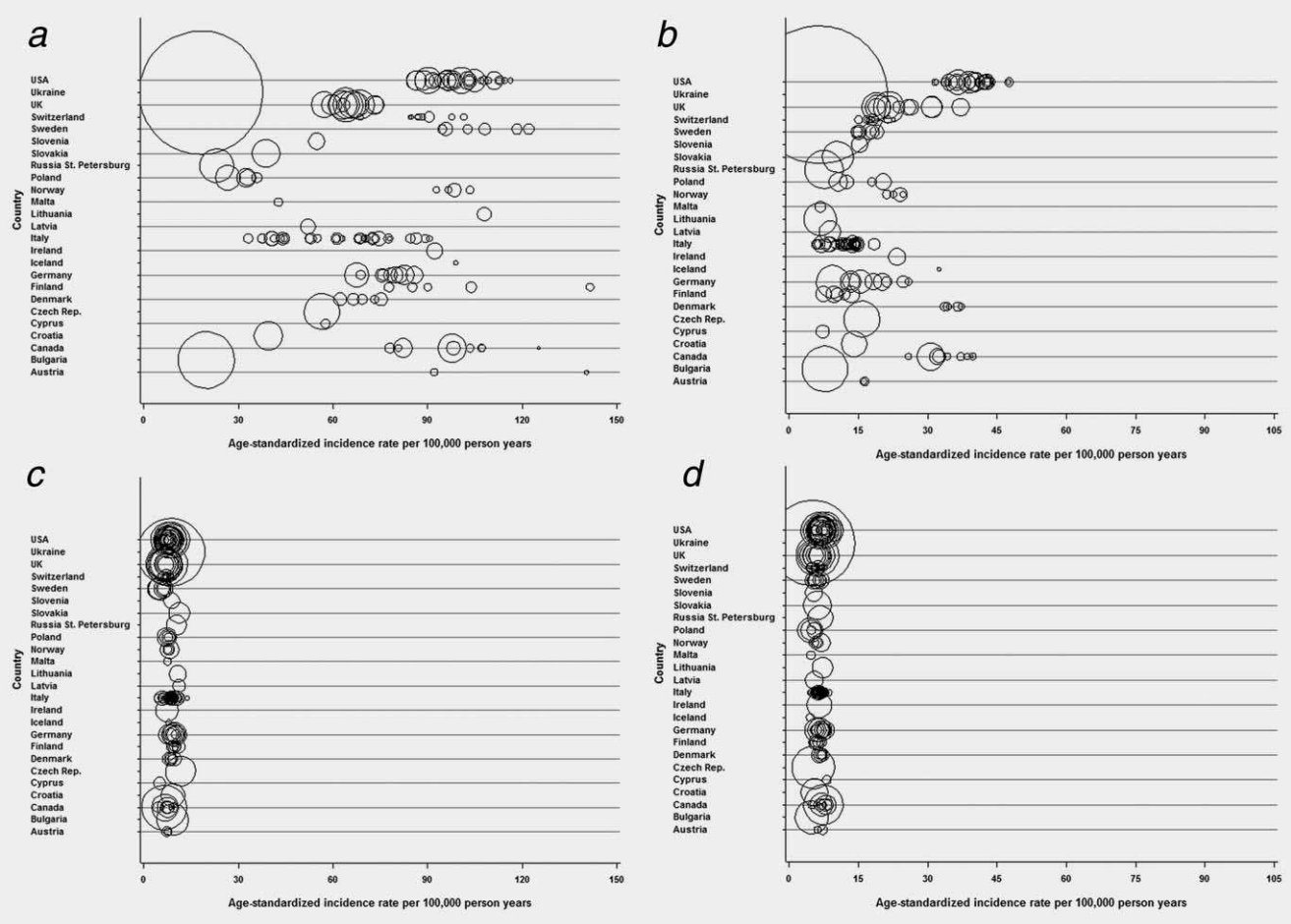

Figure 2. Distribution of cancer incidence rates of cancers with high and low intracountry correlation. (*a*) High ICC, men, prostate cancer; (*b*) high ICC, women, lung cancer; (*c*) low ICC, men, pancreas cancer; (*d*) low ICC, women, leukemia. The larger the bubbles, the higher the precision of the rate estimates.

known, our results provide a kind of proof-of-principle, that is, the weighted multilevel Poisson regression analysis produces expected and therefore credible results.

Assuming validity of this approach, the high ICC values for stomach cancer among men and thyroid cancer among women are interesting findings and warrant further investigation. The high ICC for thyroid cancer among women may be especially due to variation of the application of highly sensitive diagnostic techniques such as computed tomography scanning and ultrasonography for the diagnosis of benign diseases of the thyroid (*e.g.*, struma) between countries. The use of these techniques has a substantial influence on the magnitude of the incidence rate and overdiagnosis of papillary thyroid cancer, the most frequent thyroid cancer. The estimated proportion of overdiagnosed papillary thyroid cancers in the USA among people aged 50+ years is 41.1 and 60.1% among men and women, respectively.[15]

Calendar time may be another relevant dimension as the prevalence and distribution of population-wide risk factors is likely to vary over time. Owing to the small number of publically available regional cancer incidence estimates, we restricted our analyses to European and North American non-Hispanic white populations. Inclusion of other regions and ethnicities may provide additional insights and help to disentangle geographical and genetic (ethnic) influences on the incidence of cancer.

Recently, Tomasetti and Vogelstein stated that in 22 of 31 cancer sites, the number of stem cell divisions, which they used as a surrogate marker for random mutations arising during DNA replication in the absence of exogenous factors, correlates strongly with cancer incidences and is an important determinant of lifetime cancer risk.[16] Only for the nine remaining cancer sites did the authors suggest a major role of inherited, environmental and lifestyle factors although their results have been criticized.[17–22] Our calculation method of ICC as estimates of between-country variation may be helpful to corroborate their hypothesis. One would expect that the ICCs for cancer sites that are predominately influenced by random mutations are low, whereas cancers that are affected by lifestyle, genes or environment are high according to Tomasetti and Vogelstein. In contrast to the cancers that we included, they focused on several rare cancer

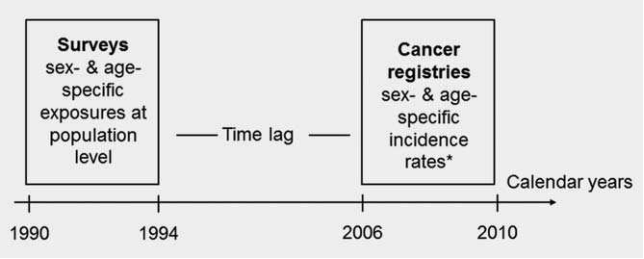

Figure 3. Design of an ecologic study that accounts for time lag and sex differences of associations. *Stratified by cancer characteristic like histology.

types, and thus, mainly included other cancer types than the ones included in our study. A systematic study on those rare cancers studied by them could provide further insights into their concept.

Our Poisson model can be generalized to include additional covariates as fixed effects or random effects. Additional random effects would yield different ICCs in, for example, different geographic regions. It is also possible to add additional spatial structure to the random effects to model neighborhood relations.[23] The choice of the standard population in the standardization of rates may influence the results of the ICC analysis. Therefore, future in-depth studies should explore rates standardized to different standards. It might be of interest that the idea of analyzing ecological data with random effects to account for clustering is not new, but has been proposed, for example, by Prentice and Sheppard[24] before. Their model does not require distributional assumptions for the random effects, resulting in a potential loss of efficiency, but also in a potential gain of robustness. In addition, Prentice and Sheppard showed that the effect of measurement error on parameter estimation is typically small.[25] Finally, it has been suggested that this model is most informative in situations where there is little individual variation in the single clusters.[26]

An ecologic cross-country study of the etiology on cancer should fulfill several features: (*i*) a reasonable time lag between initial exposure and cancer occurrence is enabled, (*ii*) ecologic analyses are stratified by sex, age and tumor characteristics such as histology and (*iii*) only countries with high-quality cancer registries and where survey data on potential risk factors are available are included. Over the last decades, many higher resource countries have established high-quality population-based cancer registries (*Cancer Incidence in Five Continents, Volume X*) and have undertaken population-based surveys on lifestyle factors and other characteristics enabling researchers to perform high-quality ecologic studies nowadays (Fig. 3). For example, the PubMed search "survey [title] AND population-based [title] AND (lifestyle OR risk factors)" (accessed on April 22, 2015) revealed 397 publications of population-based surveys from all over the world.

Our study suffers from potential limitations. Most importantly, a valid comparison of cancer incidence between regions requires that the comparability, validity and completeness of cancer registration are equally high in all regions. Although we based our study on registries that have contributed to *Cancer Incidence in Five Continents*, *Volume X* and therefore have undergone a detailed quality evaluation,[11] varying definitions, varying reporting habits and varying coding of cancers may still have had an influence on the magnitude of the incidence rates such as the inclusion of *in situ* bladder cancers in the reporting of bladder cancer. As most countries have national cancer registry groups, definition, reporting and coding of these cancers are likely to be more homogenous among regional registries within countries than registries between countries.[27] As death certificates are used to supplement cancer registries (so-called death certificate only cases), varying practices of cause of death certification between countries are likely to increase ICC especially for highly fatal cancers.[10]

In conclusion, our results indicate that the variability of cancer incidence between- and within-countries differs by cancer type and sex. The ICC could be used as a marker for future ecologic studies focusing on cross-country sex-specific variations, where cancers have a high ICC and for which screening and diagnostic activities are not plausible explanations for the between-country variations in incidence.

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