ABSTRACT

Cancer incidence data for the Ontario Public Health Units in 1980-91 were examined to investigate regional patterns and the existence of outlier values after adjustment for known risk factors. Candidate risk factors were derived from the Ontario Health Survey and the census. Weighted regressions were fit to the data, and the spatial pattern of the residuals was analyzed.

The number of outlier data points with significant elevations or reductions in risk was close to that expected by chance. They were dispersed geographically, and occurred in a variety of cancer types. We conclude that, in general, most of the geographic variation in cancer risk can be associated with variation in known risk factors, and that there appear to be no broad regional effects remaining after adjustment for these factors. A few cancer sites provide limited evidence of regional effects that may warrant further investigation.

ABRÉGÉ

Nous avons revu les données statistiques des unités de santé publique de l'Ontario (1980-91) concernant l'incidence du cancer dans le but d'identifier les déterminants potentiels des variations régionales des risques à travers la province. L'information relative aux facteurs de risque provenait de l'Enquête sur la santé de l'Ontario de 1990 et du recensement. Une régression des carrés minimisés a été effectuée, ainsi qu'une analyse des corrélations spatiales des erreurs.

Le nombre de points extrêmes résultant en une augmentation ou une réduction significative du risque se rapprochait de celui anticipé par l'effet du hasard. Géographiquement, ces extrêmes étaient distribués à travers la province et étaient observés dans plusieurs types de cancer. Ces données démontrent qu'il n'y a pas d'unités où l'on retrouve un risque de cancer anormalement élevé ou anormalement bas, comparativement à l'ensemble de la province, après ajustement pour les facteurs de risque connus. Les données concernant quelques sites suggèrent cependant la possibilité d'effets régionaux qui méritent d'être analysés davantage.

An Analysis of the Geographic Variation in Cancer Incidence and its Determinants in Ontario

Stephen D. Walter, PhD,¹ Loraine D. Marrett, PhD,²
S. Martin Taylor, PhD,³ Derek King, BMath¹

We have previously demonstrated significant spatial patterning in a variety of Ontario cancer incidence rates.¹ These findings motivated the further analysis, reported here, to investigate if additional regional effects or outlier points could be identified after adjustment for known socioeconomic, lifestyle and environmental risk factors. There are several reasons for carrying out this type of research in Ontario, including: the earlier observations of geographic patterns of cancer risk; the high quality and coverage of the Ontario Cancer Registry (OCR) data; the existence of other data sets on plausible determinants; and the large population base.

METHODS

The data employed here included: age- and sex-specific cancer incidence rates for various cancer sites, by Public Health Unit (PHU); and selected variables from the Ontario Health Survey (OHS) and the census. Ontario's PHUs are combinations of census divisions (or equivalent), and represent county-level aggregations of municipalities.

Cancer incidence data

The OCR provided the annual number of cases of each of 24 types of cancer by age group (15-19, 20-24, ..., 70-74, and 75-84 years), sex and PHU, for 1980-91. The relatively few cases aged <15 or ≥84 years were excluded to yield comparability with the OHS, as were cases with unknown residence. There were sufficient cases to give a relatively stable estimate of the incidence rate in the majority of the PHUs for most cancer sites. Sex-specific, age-standardized incidence rates were adjusted to the Ontario population using the direct method. Population denominators were obtained from the census.

Ontario Health Survey (OHS) data

The 1990 Ontario Health Survey includes extensive data on social, economic, physical, behavioural, nutritional, occupational and other factors related to health.² It was completed by 46,228 individuals aged 15-84. The population-based, cluster sample design was stratified in 42 PHUs, with the PHUs of Bruce and Grey/Owen Sound being combined. Each respondent has a study weight reflecting the probabilities of selection and non-response at the household and individual levels. The study weights were re-scaled by sex, to give analytic weights for our regressions. Due to lack of geographic accuracy in reporting cancer incidence within Metropolitan Toronto, we combined its six PHUs, giving 37 units of analysis.

Data on potential risk factors were obtained either from single questions (e.g., 'Have you ever had a mammogram?') or derived from several questions (e.g., dietary fat as a percent of total food and beverages energy consumed). Sex-specific OHS data were directly age-standardized to the

1. Department of Clinical Epidemiology & Biostatistics, McMaster University, Hamilton, Ontario
2. Division of Preventive Oncology, Cancer Care Ontario, Toronto, Ontario
3. Department of Geography, University of Victoria, Victoria, BC

Correspondence: S.D. Walter, Professor, Department of Clinical Epidemiology and Biostatistics, McMaster University, HSC-2C16, Hamilton, ON, L8N 3Z5, Tel: 905-525-9140, ext 22338, Fax: 905-529-3012, E-mail: walter@mcmaster.ca

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TABLE I
Candidate Independent Variables for Regressions: Ontario Cancer Incidence, 1980-91

Variable	Description	Source	Age Adjusted	Range of Values M F		Cancer Sites (ICD9)
Population density	population x 10 ⁻⁴ /km ²	1986 census	N	0.18-3480		All
Income	% low income households ^a	1986 census	N	6.6-19.5		All
Education	% < grade 9	1991 census	Y	5.7-20.7	6.6-20.7	All
Employment	% in industry ^b	1991 census	Y	15.7-55.4	3.0-22.3	All
	% semi-skilled/unskilled labourer ^c	OHS	Y	32.1-49.7	41.3-62.6	All
	% farming ^d	OHS	Y	0.09-23.7	0-13.3	140; 172; 200, 202; 203
Immigration	% not born in Canada	1991 census	Y	6.1-49.9		150, 151, 180
	% not born in Canada, USA or W. Europe	1991 census	Y	1.2-41.3		150, 151, 180
Smoking	% ever smoked cigarettes	OHS	Y	51.4-74.3	42.4-66.4	140; 141-49; 150; 151; 157; 161; 162; 180; 182; 185; 188; 189; 193; 204-208
	mean pack-years ^e	OHS	Y	11.1-22.0	5.2-11.8	140; 141-49; 150; 151; 157; 161; 162; 180; 182; 185; 188; 189; 193; 204-208
Diet	% current pipe/cigar smokers	OHS	Y	12.6-25.6	1.9-7.0	140; 141-149; 153-154
	fat-mean kg/day	OHS	Y	0.09-0.13	0.08-0.09	153-154; 156; 174; 182; 183; 185
	fat as % total energy intake	OHS	Y	35.9-40.5	34.6-38.1	153-154; 156; 174; 182; 183; 185
	fruit/vegetable - mean servings/day	OHS	Y	4.7-5.5	4.6-5.4	141-149; 150; 151; 153-154; 157; 161; 188
Alcohol	coffee - mean cups/day	OHS	Y	1.3-2.5	1.3-2.1	157; 188
	% > 12 drinks/week	OHS	Y	0.7-5.2	0.0-2.7	141-149; 150; 153-154; 157; 161; 174
Obesity/exercise	% BMI > 27 ^f	OHS	Y	23.6-37.5	15.2-31.7	153-154; 156; 174; 182; 189
	% inactive ^g	OHS	Y	13.6-33.6	16.2-31.3	153-154
	mean energy expenditure (kcal/kg/day) ^h	OHS	Y	2.6-4.4	2.4-3.6	153-154
Occupational Exposures ⁱ	% glass fibres, dust or asbestos (past year)	OHS	Y	5.8-22.6	0.53-2.5	150; 151; 161; 162
	% metal fumes/dust (past year)	OHS	Y	3.9-17.7	0.4-2.9	141-149; 150; 151; 156; 161; 162; 185; 203
	% solvent, paint or gasoline fumes (past year)	OHS	Y	19.7-52.9	6.6-17.4	141-149; 150; 151; 157; 188; 189; 191-192; 203; 204-208
	% coal tar/pitch (past year)	OHS	Y	2.9-11.5	0.1-1.4	151; 162
	% pesticides (past year)	OHS	Y	4.6-32.8	1.0-8.5	156; 200, 202; 203
Sexual/reproduction	% wood, grain, hay or straw dust (past year)	OHS	Y	13.3-53.6	1.7-14.8	201
	% < 15 at first intercourse	OHS	Y	-----	18.8-36.5	180
	% > 2 sex partners (past year)	OHS	Y	-----	0.4-3.5	180
	% no births	OHS	Y	-----	20.1-37.8	174; 182; 183; 201
	% using oral contraceptives	OHS	Y	-----	17.6-27.6	174; 182; 183; 193
	% using other female hormones	OHS	Y	-----	4.7-14.3	174; 182; 193
Disease Detection	% Pap test (past 2 years)	OHS	Y	-----	57.2-75.0	180
	% ever had mammogram	OHS	Y	-----	23.1-41.4	174
	% breast exam (past 12 months) ^j	OHS	Y	-----	34.0-53.4	174
Sunlight	latitude (°N) ^k	other	N	42.2-49.7		140; 172
	% > 1 hour of outdoor activity (past month)	OHS	Y	30.5-51.8	19.2-31.1	140; 172

a Low income is defined by Statistics Canada on the basis of household income and size

b Industry includes farming, forestry, mining, etc.; processing, machining and product fabricating, assembling and repairing; and construction

c Longest job as skilled/semi-skilled labourer

d Longest job in farming

e Never smokers have pack-years = 0

f BMI = body mass index: kg/m²

g Usual daily activities described as mostly sitting/inactive

h Based on physical activities during the previous month

i Categorized into two levels: ≥ occasionally exposed and ≥ often exposed. Ranges are given only for occasional exposure

j Breast exam done by physician or nurse

k Latitude of largest population centre of PHU

Ontario population, based on proportions for discrete risk factors and means for continuous ones, using the same age categories as the cancer data.

Census data

Data on socioeconomic status and the residential environment were taken from the census. The 1986 census was approximately

at the midpoint of the cancer data, and thus provides "typical" values for the study period. However some 1986 variables were not available by sex or age, and so could not be standardized. Preliminary investigation suggested that the analysis might be substantially biased by using unstandardized data. Accordingly, sex-specific 1991 census data on education (less than grade 9), immigra-

tion and occupation were adopted and age-standardized. We also included 1986 data on population density and low income, but these were not standardized or sex-specific, because they are not based on individual level observations. Data on latitude were based on our earlier work.¹

Table I summarizes the candidate risk factors for our analyses, including the data

TABLE II
Summary of Regressions on Geographic Variation of Cancer Incidence
in Ontario, 1980-91

Site (ICD 9 Code)	Sex	Number of Cases	Model R ²	Spatial Auto-correlation	
				Log (incidence)	Regression Residuals
Lip (ICD9 140)	M	1854	0.73	0.14	0.14
Oral cancer (ICD9 141-149)	F	372	0.41	-0.12	-0.22
Esophagus (ICD9 150)	M	3781	0.42	-0.16	-0.10
Stomach (ICD9 151)	F	2008	0.45	-0.09	-0.21
Colorectal (ICD9 153-154)	M	2808	0.51	0.12	0.03
Gallbladder (ICD9 156)	F	1163	0.48	-0.02	-0.22
Pancreas (ICD9 157)	M	6844	0.83	0.38	-0.16
Larynx (ICD9 161)	F	3791	0.73	0.39	-0.01
Lung (ICD9 162)	M	28,052	0.41	0.18	0.04
Melanoma (ICD9 172)	F	25,382	0.44	0.24	0.18
Breast (ICD9 174)	M	1169	0.30	0.03	0.08
Cervix (ICD9 180)	F	1780	0.14	0.10	0.10
Uterus (ICD9 182)	M	5141	0.49	0.19	-0.16
Ovary (ICD9 183)	F	4419	0.50	0.11	-0.07
Prostate (ICD9 185)	M	3852	0.70	0.19	0.16
Testis (ICD9 186)	F	744	0.49	0.10	-0.05
Bladder (ICD9 188)	M	33,086	0.84	0.52	-0.06
Kidney (ICD9 189)	F	15,176	0.69	0.66	0.29
Central Nervous System (ICD9 191-192)	M	4863	0.59	0.39	-0.04
Thyroid (ICD9 193)	F	4791	0.49	0.41	0.09
Non-Hodgkin's Lymphoma (ICD9 200,202)	M	50,254	0.40	-0.06	0.15
Hodgkin's Disease (ICD9 201)	F	5826	0.39	0.38	0.13
Multiple Myeloma (ICD9 203)	M	11,524	0.67	0.42	-0.05
Leukemia (ICD9 204-8)	F	8342	0.23	-0.12	-0.09
	M	20,171	0.30	0.34	0.09
	F	2556	0.19	0.17	0.08
	M	12,808	0.19	0.11	0.05
	F	4170	0.33	-0.04	-0.16
	M	6296	0.10	-0.15	-0.19
	F	3830	0.41	0.16	0.01
	M	4566	0.32	-0.14	-0.16
	F	3786	0	-0.12	—
	M	1088	0.51	0.04	-0.09
	F	3229	0.67	0.35	0.25
	M	7708	0.40	-0.08	-0.12
	F	6385	0.11	0.15	0.07
	M	1950	0.10	-0.12	-0.10
	F	1500	0	-0.16	—
	M	2642	0.19	0.01	-0.07
	F	2305	0.17	-0.20	-0.23
	M	6913	0.51	0.30	0.24
	F	5085	0.29	0.23	0.13

R² = multiple correlation squared

Spatial auto-correlation measures relationship between values in neighbouring PHUs (see text for details)

source, the range of observed values, and the cancer sites for which they were considered. Our specification of candidate variables was guided by recent literature on cancer etiology (e.g., references 3 and 4). Our focus was on socioeconomic and lifestyle factors, but certain occupational factors were also included for some types of cancer.

ANALYSIS

For each risk factor, summary statistics were computed to ascertain their variability

and skewness, and to identify rarely used response categories and outlying values. Our dependent variable was the log (base 10) of the directly standardized rate in a PHU. Use of the log transformation yielded approximate normality in the data. Each PHU was weighted according to its population size, to allow for different levels of sampling variation in the observations.

For each cancer site, candidate risk factors were included in a stepwise backwards elimination regression. A significance level of 0.10 was required for a factor to be

retained in the final model. The regressions were summarized using: the spatial auto-correlations (SACs) of the log incidence rates and the residuals; the overall R² value for the final model; the regression coefficient, standard error and partial p-value for each significant term. Additional regressions (not reported here) were also fitted in which the spatially correlated error structure was modelled directly. Further details of our regression methods are provided elsewhere.⁵

The SAC for the cancer rates measures the degree of geographic clustering observed in the cancer incidence data, without adjustment for any risk factors. It was evaluated over pairs of neighbouring PHUs, i.e., PHUs having a common geographic boundary. The residuals reflect the difference between the observed incidence and the expected incidence after adjustment for factors in the regression. High SAC values for the residuals would suggest additional regional effects, not explained by the regressions. We anticipated that the SAC would be typically lower for the residuals than for the incidence. We also anticipated the SAC for incidence to be positive, reflecting determinants of risk in neighbouring PHUs. Negative SAC values would either be due to sampling variation or would not plausibly reflect environmental effects, because they would correspond to situations where areas of high risk tended to border areas of low risk, and vice versa. R² can be interpreted as the proportion of variation in incidence that is associated with (or "explained" by) the factors in the regression.

The residuals were mapped to try to identify regions or specific points where the incidence was notably above or below the model expectation, thereby suggesting local environmental or other effects. We also considered the most extreme outliers individually.

RESULTS

We will first present an overall assessment of the spatial patterns in the incidence data and the residuals, and then examine the outliers. Table II shows the number of cases, the model R², and the SAC in the log incidence rates and the

residuals, for each cancer site. The spatial pattern in incidence was strongest for lung cancer, in both males and females (SAC = 0.52 and 0.66, respectively). Moderate geographic clustering (SAC values greater than 0.2) were observed for stomach cancer in both males and females, male and female melanoma, cervical cancer, uterine cancer, prostate cancer, female thyroid and colo-rectal cancer, and male and female leukemia. The regional effects in incidence for other cancer sites were more modest.

Only three regressions produced residual SACs greater than 0.2: female lung cancer (0.29), female thyroid cancer (0.25) and male leukemia (0.24). Elsewhere the small (sometimes negative) residual SAC values suggest that any regional effects had been taken account of by the regression variables. More extensive details of the site-specific risk factor results are shown in a related publication.⁵

We examined the residuals from all the regressions in order to identify locations where adjusted cancer risks might be particularly high or low. Because the number of combinations of PHUs with cancer sites was large, we adopted a stringent definition of an outlier, specifically, that the studentized residual (the ratio of the residual to its standard error) should be greater in absolute value than its 99th percentile value (2.57). Theoretically, if all of the relevant factors had been identified in the regressions, additional variation would be entirely due to chance, and we would then expect 1% of the fitted data points to be defined as outliers.

Table III lists the 15 observed outliers, so defined. The total number of data points in the entire set of regressions was 37 (PHUs) x 42 (sex/cancer site combinations) = 1554; therefore, the number of outliers expected by chance alone would be 1554×0.01 , or approximately 15.5, which agrees closely with the observed number. Five of the outliers represent PHUs where the incidence is higher than expected from the model, and 10 where the risk is lower. Eight points refer to male data and 7 to female data.

There is no obvious geographic pattern in the locations of the outliers; most of the PHUs shown in Table III have only one entry, and they are widely distributed

TABLE III
Outlier Data Points Identified by Regression Analysis

Cancer	Sex	PHU	Studentized Residual	Number of Cases	SIR	SIRadj
Lip	F	Niagara	-3.00	5	0.29	0.47
Oral cancer	M	Timiskaming	-3.00	6	0.33	0.38
Esophagus	F	Peterborough	-3.19	6	0.35	0.52
Colorectal	F	Niagara	-2.83	1078	0.90	0.88
Gallbladder	F	York	-2.70	28	0.59	0.70
Larynx	M	North Western	-2.79	22	0.62	0.65
Melanoma	M	Hastings	2.59	97	1.27	1.37
		Middlesex	-2.85	145	0.83	0.81
Prostate	M	Durham	2.77	766	1.31	1.26
Testis	M	Algoma	-3.10	18	0.50	0.54
		Haliburton	-2.57	24	0.61	0.61
Kidney	F	Huron	-3.43	14	0.51	0.52
CNS	M	Sudbury	2.62	124	1.27	1.22
Multiple Myeloma	M	Waterloo	2.84	122	1.23	1.43
Leukemia	F	Halton	3.00	164	1.18	1.36

SIR = standardized incidence ratio

SIRadj = ratio of observed to expected standardized incidence ratios, adjusted for regression variables.

around the province. Table III also shows the standardized incidence ratio (SIR) (the ratio of the directly adjusted rate in the PHU to the rate for Ontario as a whole) and the regression-adjusted SIR (the ratio of the expected cancer incidence relative to Ontario, taking the effects of the regression variables into account). The regression-adjusted SIRs are typically quite close to the original incidence SIRs. We conclude that the apparent risk differences in the outlier points appear to be unassociated with the risk factors identified in the regressions, and they may in fact be completely random. The 5 outlier risk elevations have SIR values 1.27, 1.31, 1.27, 1.23, and 1.18. When one recalls that these are the statistically most extreme values from a distribution of 1554 points, they represent rather modest risk increases.

In summary, given: (i) the dispersed pattern of occurrence of the outliers; (ii) their lack of grouping by cancer type; (iii) the close agreement of the observed number of outliers with the number expected by chance; and (iv) their generally modest elevations in risk, a reasonable interpretation is that most if not all of the extreme values are due to chance.

CONCLUSION

The geographic pattern of health data is often used by epidemiologists as a means of surveillance of the entire population or to identify local anomalies. Examples include national and regional atlases of

mortality and morbidity,⁶⁻⁹ and analyses of variation in health associated with socioeconomic factors, environmental variables, screening programs or utilisation of health care.¹⁰⁻¹⁸

The results of our Ontario analysis presented here suggest that there are no regions with exceptionally deviant risks of cancer, once known risk factors are taken into account. Cases where both the incidence rates and the residuals showed slightly stronger spatial correlation values (greater than 0.2) were: male leukemia; female lung cancer; and female thyroid cancer. These may be cancers with continuing research interest, to investigate the unexplained regional effects. Otherwise, the results indicate that the geographic variation in cancer incidence can be somewhat explained by known lifestyle and socioeconomic factors. After adjustment for these factors, there was no strong indication of additional regional effects on cancer risk.

This study had strength in its wide geographic scope and in the comprehensiveness and quality of its data. On the other hand, one must accept that only relatively weak inferences about individual risk are possible from geographically aggregated data of this type.¹⁹⁻²² Also, the study was designed to investigate broad geographic trends, rather than as a mechanism for evaluating risk in specific locations. A highly localized environmental effect acting on the residents of only one PHU would not lead to geographic patterns in the province-wide data. While the number

of nominally outlying data points was close to its expectation by chance alone, we cannot preclude the possibility of localized effects with an environmental origin.

In summary, the overall message to public health administrators is reassuring, that once we take known risk factors into account, there appears to be no evidence of strong differences in cancer risk in Ontario that would be expected if environmental factors (e.g., related to air or water quality) were operative at a regional scale. Nevertheless, the need for vigilance at the local level remains.

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