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Clustering of concordant and discordant cancer types in Swedish couples is rare

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ABSTRACT

Background: Spouses are exposed to common environmental cancer risk factors during adulthood. Investigating the aggregation of cancer in couples might provide valuable insights into cancer development.

Methods: The 2008 update of the Swedish Family-Cancer Database includes over 2 million couples with at least one child in common with one single partner. We quantified the contribution of shared adulthood environment by standardised incidence ratios (SIRs) and population attributable fractions (PAFs). Estimated SIRs were used to build an etiological map reflecting the similarity of cancers by adult environmental exposures.

Results: Increased risks of concordant types amongst spouses were found for lung, upper aerodigestive tract and skin cancers (SIRs from 1.24 to 1.97),which are probably related to shared exposure to smoking and UV radiation. PAFs were low with the highest value of 1.46% for uterus cancer in wives of men affected by prostate cancer. Further analysis, based on all non-sex-specific concordant and discordant types, revealed a clustering of lung, stomach, pancreas and bladder cancers sharing smoking as a risk factor. This aggregation was used as a cut-point to identify further "novel" clusters.

Conclusion: Shared lifestyles including smoking and drinking habits as well as human papilloma virus infection (HPV) might be associated with an excess of cancer incidence amongst spouses. We observed significantly an increased risk for smoking-related cancers such as lung, upper aerodigestive tract and oesophageal cancers. The present population-based study confirms that the lifestyle shared by spouses plays a minor role in cancer causation. Only strong environmental risk factors such as smoking seem to influence cancer development in adulthood. The proposed etiological map based on 24 cancer types identifies novel clusters – for example, non-Hodgkin lymphoma and leukaemia, bone cancer and myeloma – that are not completely explained by established risk factors. Some of the identified clusters relied on reproduced associations between cancer risks amongst husband and wives; however, the role of chance cannot be excluded.

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1. Introduction

Decades of cohabitation may result in a common lifestyle and health behaviour amongst spouses. Significant concordance has been found between spouses for body mass index, history of smoking, physical exercise and diet.[1–4] A partner's smoking status has been shown to influence the spouse's smoking initiation and cessation.[1,5] A similar effect has been observed regarding alcohol consumption.[6] Previous studies have shown that the spousal similarities may also be explained by assortative mating: individuals prefer partners who are similar to themselves across a wide range of characteristics such as personality, leisure interests, health and smoking.[7,8] As a consequence, assortative mating and shared marital lifestyles, for example dietary habits, tobacco use and alcohol consumption, may result in concordance of disease amongst spouses.[9]

Studies on genetically unrelated spouses might provide valuable insights on the contribution of environmental factors in cancer etiology and additionally can be used in the apportionment of heritable effects. Earlier studies have evaluated the association between cancer and common lifestyle factors in spouses. Significant spousal concordances have been found for some cancer types (cancer of the lung, pancreas, bladder, tongue, stomach, non-Hodgkin lymphoma and melanoma). Tobacco is surely responsible for some of the observed concordance, but also other environmental factors such as Helicobacter pylori infections, dietary deficiencies, UV exposure and alcohol consumption have been discussed as etiological candidates.[10–16] Based on the cluster of cancer types with established environmental factors we aimed to identify further ones with common yet unknown risk factors.

The present study is based on the latest update of nationwide Swedish Family-Cancer Database that includes cancers from the Swedish Cancer Registry recorded between 1958 and 2006. The study aims to quantify the contribution of spousal environmental sharing to a cancer risk, and to explore the clustering of cancer types amongst spouses. We defined "spouses" as individuals who had at least one child in common with only one partner. This is a more stringent criterion than the definition used in previous spouse-based studies.[10] We systematically analysed the risk for all concordant and discordant cancer types and summarised this information by an etiological map.

2. Materials and methods

Statistics Sweden created a family database, the "Second Generation Register" in 1995, which after a few expansions was renamed as "Multigeneration Register" in order to reflect the availability of more than two generations in the database.[17] In 2008 this registry was linked for the eighth time to the Swedish Cancer Registry, covering cancers from 1958 to 2006, to create the Swedish Family-Cancer Database. This latest update includes all persons born in 1932 and later with their biological parents, totalling over 11.8 million individuals. Additionally, residential and socio-economic data are available from national censuses, which were carried out in 1960, 1970, 1980 and 1990. The Swedish Cancer Registry is based on compulsory nationwide notification of cases by clinicians, pathologists and cytologists and the completeness of registration is considered to be close to 100%.[18] Four-digit diagnostic codes from the seventh revision (ICD-7) of the International Statistical Classification of Diseases[19] and the subsequent ICD classifications are available. However, for reasons of comparability with earlier years, codes were translated to ICD-7. The following cancers and their corresponding three digit ICD-7 codes were included in our analysis: upper aerodigestive tract (140, 141, 143-148 and 161), oesophagus (150), stomach (151), small intestine (152), colon (153), rectum (154), liver (155 and 156), pancreas (157), nose (160), lung (162 and 163), breast (170), cervix (171), endometrium (172), uterus (173), ovary (175), other and unspecified female genital organs (176), prostate (177), testis (178), other and unspecified male genital organs (179), kidney (180), urinary bladder (181), melanoma (190), skin, squamous cell (191), eye (192), nervous system (193), thyroid gland (194), endocrine glands (195), bone (196), connective tissue (197), non-Hodgkin's lymphoma (200 and 202), Hodgkin's disease (201), myeloma (203) and leukaemia (204-209).

Spouses were defined as individuals with common biological descendents. Individuals with multiple partners were not included in the study. Follow-up started at the year of immigration, birth year or the start year of the cancer registry, whichever came latest. Follow-up was terminated on diagnosis of the first cancer, death, emigration or end of the study (December 31, 2006). Standardised incidence ratios (SIRs) were used to quantify spousal relative risks of cancer. SIRs, estimated as the ratio of the number of observed to expected cases, were calculated for both concordant and discordant cancer types. Expected numbers were obtained from 5-year age-, sex-, 5-year period-, socio-economic status- (6 groups), and region- (4 groups) specific incidence rates. Confidence intervals (95% CIs) were derived under the assumption of a Poisson distribution.[20] The investigation of multiple type combinations may result in false positive associations. To alleviate this problem, associations were reported according to 0.05 and after controlling for multiple testing with the Benjamini–Hochberg method.[21]

We also estimated the population attributable fractions (PAFs) based on the inferred SIRs. In the present study, the PAF represents the proportion of cancer cases that is attributable to having a husband/wife diagnosed with cancer, that is the relative increase/decrease in cancer incidence if the population did not include individuals with affected spouses. PAFs were calculated according to the formula $p_e(SIR - 1)/(p_e(SIR - 1) + 1)$, where p_e was the prevalence of exposure in the population investigated. Confidence intervals for PAFs were estimated by bootstrapping based on 1000 iterations.[22]

To quantify the clustering of cancer in spouse pairs, we calculated a distance matrix amongst all the investigated cancer types excluding sex-specific malignancies. The distance matrix relied on the ranking of SIRs. Two SIRs were observed for concordant types and four SIRs were available for discordant cancers, e.g. lung/bladder cancer in husband/wife. To compute ranks, we first randomly selected one SIR and sampled from its distribution. After sampling for any type combination, SIRs were ranked in a reverse order. Mean ranks

were assigned to tied values. The distance between the cancer types was finally calculated as the corresponding rank divided by the number of investigated type combinations. This procedure was iterated 10,000 times using SAS Version 9.2 in order to generate an average distance matrix, which was represented as a dendrogram and heatmap using the function HCLUST with the average linkage method and heatmap.2 in the R Version 2.9.1.[23,24]

The Swedish Family-Cancer Database was approved by the Lund regional ethical committee on 8/12/2008 (No. 409/2008) and with complementary approvals dated 9/1/2009 and 1/22/2010.

3. Results

The Swedish Family-Cancer Database included over 2.5 million men and women with common biological descendents with only one partner. These individuals were defined as spouses in our analysis. Women contributed over 102 million person-years at risk and 369,174 cancer cases. There were 93,596 cancer cases amongst wives of cancer patients. Men contributed over 97 million person-years at risk and over 406,741 cancer cases. There were 93,596 cancer cases amongst men with an affected wife (Table 1).

Table 2 shows SIRs in men with affected wives for both the concordant and discordant cancers. SIRs in women with affected husbands are shown in Table 3. We systematically analysed any combination of cancer types. Due to the large amount of data, only the highest and second highest SIRs based on at least five observations are presented in Tables 2 and 3. PAFs are also shown. Significantly increased SIRs at the 0.05 confidence level are made bold In this study, we particularly focused on significant findings after controlling for multiple testing, which are underlined in Tables 2 and 3. The small risk-excesses in spouses of cancer patients translated into low PAFs. The highest PAF observed in males related to other and unspecified genital cancer in husbands of breast cancer patients (PAF 0.70%). The highest PAF in females related to uterus cancer in wives of prostate cancer patients (PAF 1.46%).

Significantly increased risks for concordant sites were found for lung cancer in husbands (SIR 1.42 and PAF 0.20%) and wives (SIR 1.38 and PAF 0.52%) (Tables 2 and 3). Husbands were at a significantly increased risk of colon cancer when the partner was affected by eye cancer (SIR 1.84) and vice versa (SIR 1.87 for eye cancer in wives of men with colon cancer). Husbands of women with cervical cancer had an increased risk of upper aerodigestive tract cancer (SIR 1.41) (Table 2). Wives showed an increased risk of cervical cancer when husbands were affected by upper aerodigestive tract cancer (SIR 1.33, result not shown in Table 3). A significantly increased risk for melanoma was observed in wives of husbands with skin cancer (SIR 1.24). Men with a wife affected by skin cancer showed an increased melanoma risk.

Fig. 1 represents the clustering of cancer types according to the defined distance matrix, based on any estimated non-sex-specific SIR. The dendrogram and heatmap reflect the aggregation of cancer types which resulted in increased SIRs. We found that lung, stomach, pancreas and bladder cancer built a cluster. Since these four cancer types share smoking as a relevant common environmental risk factor, we used the degree of similarity amongst these four sites (vertical dashed line on the dendrogram) to define further clusters, which are highlighted in the heatmap. The six following groups of cancer types were identified: (1) upper aerodigestive tract, nose and connective tissue, (2) bone and myeloma, (3) colon, eye and endocrine glands, (4) melanoma, skin and nervous system, (5) non-Hodgkin's lymphoma and leukaemia and (6) small intestine, thyroid gland, liver, kidney and Hodgkin's disease. Rectum and oesophagus cancer were not included in any of the clusters above.

4. Discussion

Spouses are usually genetically unrelated and share a common living environment. Thus, disease concordance in spouses mainly reflects environmental etiological contributors and may give us information on the magnitude of the influence of environmental factors. Using the 2008 update of the Swedish Family-Cancer Database we identified over 2 million individuals with one or more children in common. These individuals were defined as "spouses" in the present study. We estimated the degree of environmental causation in cancer by calculating standardised incidence ratios (SIR) for concordant and discordant cancers in spouses. Furthermore, we calculated distances between the cancer types to draw an etiological map reflecting shared adult environmental exposures. Another definition of spouses would be possible not only taking into account common children but also the length of cohabitation. This would better reflect the environmental sharing amongst spouses. However, the duration/degree of cohabitation or measures relating to the relationship of spouses (e.g. closeness and marital satisfaction) were not available in our dataset, and this was a limitation of the study. Nevertheless, less than 0.1% of all the cancer cases occurred before the birth of the first child, that is before the start of the spousal relationship according to our definition. For example, if couples separate during the follow-up period, this

Table 1 – Number, person-years and cancer cases for men and women who had at least one child in common with only one partner.

	All			With conjugal cancer history	
	Persons	Person-years	Cancer cases	Person-years	Cancer cases
Men	2,690,185	97,442,530	406,741	12,787,786	93,596
Women	2,690,185	102,470,000	369,174	15,969,527	93,596
All	5,380,370	199,912,530	775,915	28,757,313	187,192

Table 2 – SIR for concordant and discordant cancer in husbands according to cancer in wives.

Cancer in wife	Concordant cancer in husband					Discordant cancer in husband											
						Highest risk					Second highest risk						
	Obs	SIR	95% CI	PAF (%)	95% CI		Obs	SIR	95% CI	PAF (%)	95% CI		obs	SIR	95% CI	PAF (%)	95% CI	Exposed*
Bladder	177	**1.18**	(1.01;1.37)	0.05	(0.01;0.09)	Nose	6	1.38	(0.51;3.01)	0.11	(−0.11;0.55)	Small int.	13	1.36	(0.72;2.32)	0.11	(−0.05;0.36)	7704
Bone	–			–		Myeloma	6	**3.24**	(1.19;7.05)	0.05	(0.01;0.14)	Melanoma	7	1.93	(0.78;3.97)	0.02	(0.00;0.06)	607
Breast	39	1.06	(0.75;1.45)	0.28	(−0.72;1.70)	Other male gen.	95	1.19	(0.97;1.46)	0.70	(−0.06;1.49)	Nose	57	1.16	(0.88;1.50)	0.69	(−0.20;1.71)	102915
Cervix	–			–		Other male gen.	14	1.51	(0.83;2.54)	0.25	(−0.03;0.70)	Upper aer.	123	**1.41**	(1.17;1.68)	0.20	(0.10;0.32)	13176
Colon	567	1.04	(0.95;1.13)	0.04	(−0.04;0.11)	Bone	15	1.45	(0.81;2.39)	0.49	(−0.07;1.34)	Breast	16	1.40	(0.80;2.27)	0.43	(−0.11;1.22)	27816
Connective tis.	4	1.11	(0.30;2.84)	0.01	(−0.05;0.16)	Liver	19	1.44	(0.87;2.24)	0.04	(0.00;0.10)	Stomach	35	1.21	(0.84;1.69)	0.02	(−0.01;0.05)	2398
Endocrine gl.	22	1.04	(0.65;1.58)	0.01	(−0.09;0.18)	Hodgkin	18	**1.70**	(1.01;2.68)	0.23	(0.04;0.51)	Small int.	16	1.54	(0.88;2.50)	0.18	(0.00;0.49)	9029
Endometrium	–			–		Eye	29	**1.70**	(1.14;2.45)	0.56	(0.19;1.07)	Testis	29	1.40	(0.94;2.01)	0.32	(−0.01;0.75)	22070
Oesophagus	7	1.73	(0.70;3.56)	0.03	(−0.01;0.13)	Upper aer.	22	**1.97**	(1.23;2.98)	0.05	(0.02;0.10)	Oesophagus	7	1.73	(0.70;3.56)	0.04	(−0.01;0.13)	1394
Eye	1	1.29	(0.03;7.19)	0.01	(−0.03;0.46)	Colon	35	**1.84**	(1.28;2.56)	0.03	(0.02;0.06)	Nervous sys.	11	1.71	(0.85;3.05)	0.03	(0.00;0.08)	1092
Hodgkin's dis.	1	0.55	(0.01;3.04)	−0.03	(−0.06;0.25)	Oesophagus	8	**2.33**	(1.00;4.59)	0.09	(0.02;0.22)	Kidney	16	1.44	(0.82;2.34)	0.03	(0.00;0.08)	1752
Kidney	80	0.98	(0.78;1.22)	−0.01	(−0.07;0.05)	Testis	11	1.51	(0.76;2.71)	0.17	(−0.04;0.56)	Eye	10	1.46	(0.70;2.69)	0.16	(−0.06;0.50)	9009
Leukemia	65	0.94	(0.72;1.20)	−0.02	(−0.08;0.06)	Other male gen.	11	1.47	(0.74;2.64)	0.16	(−0.04;0.55)	Non-Hodgkin l.	90	**1.31**	(1.05;1.61)	0.11	(0.04;0.18)	9150
Liver	86	1.2	(0.96;1.48)	0.06	(−0.02;0.16)	Breast	9	2.16	(0.99;4.10)	0.45	(−0.01;1.17)	Hodgkin	19	1.43	(0.86;2.23)	0.18	(−0.02;0.50)	10691
Lung	520	**1.42**	(1.30;1.55)	0.20	(0.15;0.26)	Nose	11	1.41	(0.71;2.53)	0.25	(−0.10;0.85)	Oesophagus	55	**1.38**	(1.04;1.79)	0.22	(0.06;0.41)	15222
Melanoma	104	1.06	(0.87;1.29)	0.05	(−0.03;0.16)	Breast	7	1.62	(0.65;3.33)	0.32	(−0.09;1.10)	Skin	160	**1.23**	(1.04;1.43)	0.12	(0.04;0.20)	13819
Myeloma	12	0.6	(0.31;1.05)	−0.07	(−0.11;0.01)	Other male gen.	8	1.96	(0.85;3.86)	0.17	(−0.01;0.46)	Thyroid gl.	10	1.94	(0.93;3.57)	0.17	(0.00;0.43)	4676
Nervous sys.	67	0.92	(0.71;1.17)	−0.03	(−0.12;0.07)	Testis	25	**1.71**	(1.11;2.53)	0.33	(0.09;0.67)	Hodgkin	20	1.41	(0.86;2.18)	0.20	(−0.02;0.53)	12842
Non-Hodgkin l.	92	1.19	(0.96;1.46)	0.07	(0.00;0.15)	Testis	13	1.37	(0.73;2.34)	0.13	(−0.06;0.43)	Leukemia	90	1.18	(0.95;1.45)	0.07	(−0.01;0.15)	10019
Nose	–			–		Kidney	9	**2.36**	(1.08;4.47)	0.02	(0.01;0.06)							471
Other fem. gen.	–			–		Small int.	7	1.96	(0.79;4.03)	0.11	(0.00;0.33)	Endocrine gl.	12	1.84	(0.95;3.21)	0.09	(0.00;0.22)	4001
Ovary	–			–		Breast	12	1.64	(0.85;2.87)	0.45	(−0.01;1.23)	Eye	22	1.58	(0.99;2.39)	0.43	(0.00;0.90)	19210
Pancreas	91	1.22	(0.99;1.50)	0.07	(0.00;0.14)	Endocrine gl.	33	**1.64**	(1.13;2.30)	0.22	(0.08;0.42)	Thyroid gl.	14	1.41	(0.77;2.37)	0.13	(−0.05;0.46)	9366
Rectum	167	0.92	(0.78;1.07)	−0.05	(−0.11;0.02)	Bone	7	1.38	(0.55;2.84)	0.22	(−0.14;1.00)	Other male gen.	15	1.24	(0.69;2.05)	0.12	(−0.10;0.46)	13854
Skin	185	**1.16**	(1.00;1.33)	0.07	(0.02;0.14)	Eye	15	1.73	(0.97;2.85)	0.31	(−0.06;0.71)	Testis	13	1.46	(0.78;2.49)	0.19	(−0.04;0.55)	11044
Small int.	2	1.11	(0.13;4.00)	0.01	(−0.04;0.21)	Non-Hodgkin l.	16	1.36	(0.78;2.21)	0.02	(−0.01;0.06)	Kidney	18	1.35	(0.80;2.14)	0.02	(−0.01;0.06)	1506
Stomach	201	1.14	(0.99;1.31)	0.05	(0.00;0.10)	Pancreas	108	**1.27**	(1.04;1.53)	0.10	(0.03;0.19)	Connective tis.	20	1.18	(0.72;1.82)	0.07	(−0.07;0.29)	10373
Thyroid gl.	7	1.48	(0.60;3.05)	0.09	(−0.04;0.37)	Connective tis.	14	**1.98**	(1.08;3.33)	0.18	(0.04;0.41)	Small int.	9	1.85	(0.85;3.51)	0.16	(−0.01;0.44)	5103
Upper aer.	31	1.04	(0.71;1.48)	0.01	(−0.04;0.05)	Connective tis.	13	**2.07**	(1.10;3.54)	0.16	(0.04;0.36)	Myeloma	22	1.43	(0.90;2.17)	0.06	(0.00;0.15)	3024
Uterus	–			–		Prostate	6	1.23	(0.45;2.68)	0.00	(0.00;0.01)							132

Abbreviations: obs = observed number of cases; CI = confidence interval; SIR = standardised incidence ratio; PAF = population attributable fraction. Connective tis. = Connective tissue; Endocrine gl. = Endocrine glands; Hodgkin's dis. = Hodgkin's disease; Nervous sys. = Nervous system; Non-Hodgkin l. = Non-Hodgkin lymphoma; Upper aer. = Upper aerodigestive tract; Other male/fem. gen. = Other and unspecified male/female genital organs; Skin = Skin, non-squamous cell; Small int. = Small intestine; Thyroid gl. = Thyroid gland. Bold type represents significance at the 5% confidence level, underlined SIRs were significant after correcting for multiple testing (Benjamini–Hochberg method).

* Number of men exposed to the risk factor, i.e. number of men with an affected wife.

Table 3 – SIR for concordant and discordant cancer in wives according to cancer in husbands.

Cancer in husband	Concordant cancer in wife					Discordant cancer in wife											
						Highest risk						Second highest risk					
	Obs	SIR	95% CI	PAF (%)	95% CI		Obs	SIR	95% CI	PAF (%)	95% CI		Obs	SIR	95% CI	PAF (%)	95% CI	Exposed*
Bladder	177	1.15	(0.98;1.33)	0.16	(−0.01;0.31)	Pancreas	216	**1.16**	(1.01;1.33)	0.16	(0.03;0.31)	Bone	10	1.15	(0.55;2.11)	0.13	(−0.36;1.06)	28066
Bone	–			–		Colon	15	1.38	(0.77;2.28)	0.01	(0.00;0.04)	Rectum	7	1.29	(0.52;2.66)	0.01	(−0.01;0.05)	794
Breast	39	1.07	(0.76;1.47)	0.00	(0.00;0.01)	Liver	9	2.11	(0.96;4.00)	0.03	(0.00;0.06)	Ovary	12	1.66	(0.86;2.90)	0.02	(0.00;0.04)	608
Colon	567	1.02	(0.94;1.11)	0.02	(−0.05;0.10)	Eye	35	**1.87**	(1.30;2.60)	0.90	(0.42;1.57)	Nose	12	1.37	(0.71;2.39)	0.37	(−0.20;1.35)	28084
Connective tis.	4	1.08	(0.30;2.78)	0.00	(−0.06;0.17)	Upper aer.	13	**2.02**	(1.08;3.45)	0.11	(0.02;0.24)	Thyroid gl.	14	**1.98**	(1.08;3.32)	0.10	(0.03;0.23)	2882
Endocrine gl.	22	1.04	(0.65;1.57)	0.01	(−0.05;0.08)	Other fem. gen.	12	1.81	(0.94;3.16)	0.13	(0.01;0.33)	Pancreas	33	**1.58**	(1.09;2.22)	0.09	(0.03;0.18)	4366
Oesophagus	7	1.71	(0.69;3.52)	0.12	(−0.02;0.39)	Hodgkin	8	**2.40**	(1.04;4.73)	0.22	(0.04;0.53)	Lung	55	**1.33**	(1.00;1.73)	0.05	(0.01;0.10)	4204
Eye	1	1.32	(0.03;7.37)	0.02	(−0.04;0.53)	Skin	15	1.72	(0.96;2.84)	0.03	(0.00;0.08)	Endometrium	29	**1.70**	(1.14;2.44)	0.03	(0.01;0.06)	1269
Hodgkin	1	0.54	(0.01;2.99)	−0.05	(−0.09;0.39)	Endocrine gl.	18	**1.70**	(1.01;2.69)	0.07	(0.01;0.15)	Kidney	16	1.41	(0.81;2.30)	0.04	(−0.01;0.11)	2493
Kidney	80	0.98	(0.78;1.22)	−0.01	(−0.10;0.10)	Nose	9	**2.23**	(1.02;4.23)	0.60	(0.11;1.59)	Hodgkin	16	1.46	(0.84;2.37)	0.23	(−0.02;0.62)	13579
Leukemia	65	0.92	(0.71;1.17)	−0.04	(−0.12;0.06)	Thyroid gl.	40	1.25	(0.89;1.70)	0.12	(−0.02;0.29)	Cervix	110	1.19	(0.98;1.44)	0.09	(0.00;0.18)	12474
Liver	86	1.14	(0.91;1.41)	0.05	(−0.02;0.12)	Connective tis.	19	1.41	(0.85;2.21)	0.14	(−0.02;0.38)	Small int.	12	1.25	(0.64;2.18)	0.08	(−0.10;0.39)	9304
Lung	**520**	**1.38**	(1.27;1.51)	0.52	(0.39;0.66)	Bone	16	1.39	(0.79;2.25)	0.59	(−0.13;1.63)	Nose	15	1.31	(0.73;2.16)	0.38	(−0.25;1.43)	37068
Melanoma	104	1.06	(0.87;1.29)	0.03	(−0.05;0.13)	Bone	7	1.84	(0.74;3.80)	0.44	(−0.03;1.31)	Eye	11	1.48	(0.74;2.64)	0.26	(−0.07;0.80)	13646
Myeloma	12	0.58	(0.30;1.01)	−0.10	(−0.15;0.00)	Bone	6	**3.11**	(1.14;6.76)	0.50	(0.10;1.31)	Upper aer.	22	1.37	(0.86;2.07)	0.09	(−0.01;0.22)	6194
Nervous sys.	67	0.89	(0.69;1.14)	−0.05	(−0.12;0.04)	Nose	5	1.76	(0.57;4.12)	0.35	(−0.10;1.29)	Uterus	1	1.75	(0.04;9.76)	0.37	(−0.36;6.67)	11743
Non-Hodgkin l.	92	1.17	(0.94;1.44)	0.08	(−0.01;0.19)	Eye	11	1.36	(0.68;2.44)	0.17	(−0.10;0.64)	Small int.	16	1.33	(0.76;2.16)	0.16	(−0.08;0.54)	13189
Nose	–			–		Lung	11	1.38	(0.69;2.47)	0.01	(−0.01;0.04)	Kidney	7	1.37	(0.55;2.82)	0.01	(−0.01;0.05)	849
Other male gen.	–			–		Myeloma	8	1.98	(0.85;3.90)	0.05	(0.00;0.14)	Leukemia	11	1.48	(0.74;2.64)	0.02	(−0.01;0.08)	12033
Pancreas	91	1.19	(0.96;1.46)	0.08	(0.00;0.17)	Myeloma	47	1.26	(0.93;1.67)	0.11	(−0.01;0.25)	Stomach	108	**1.25**	(1.02;1.51)	0.10	(0.03;0.19)	10993
Prostate	.			.		Uterus	6	1.34	(0.49;2.93)	1.46	(−1.50;7.58)	Hodgkin	112	1.21	(0.99;1.45)	0.88	(−0.01;1.76)	115124
Rectum	167	0.90	(0.77;1.05)	−0.07	(−0.15;0.02)	Upper aer.	61	1.22	(0.94;1.57)	0.16	(−0.01;0.39)	Nose	7	1.17	(0.47;2.41)	0.13	(−0.29;0.98)	19433
Skin	**185**	**1.16**	(1.00;1.34)	0.11	(0.02;0.21)	Melanoma	160	**1.24**	(1.06;1.45)	0.16	(0.05;0.27)	Hodgkin	17	1.18	(0.68;1.88)	0.12	(−0.15;0.53)	17609
Small int.	2	1.10	(0.13;3.96)	0.00	(−0.05;0.26)	Other fem. gen.	7	1.95	(0.78;4.01)	0.06	(0.00;0.19)	Thyroid gl.	9	1.83	(0.84;3.47)	0.06	(0.00;0.16)	1918
Stomach	201	1.12	(0.97;1.28)	0.09	(0.00;0.19)	Eye	18	1.31	(0.78;2.07)	0.24	(−0.09;0.71)	Connective tis.	35	1.18	(0.82;1.64)	0.14	(−0.08;0.40)	20157
Testis	–			–		Nervous sys.	25	**1.69**	(1.09;2.50)	0.10	(0.03;0.20)	Kidney	11	1.49	(0.74;2.66)	0.06	(−0.02;0.22)	3820
Thyroid gl.	7	1.47	(0.59;3.03)	0.04	(−0.02;0.15)	Myeloma	10	1.95	(0.94;3.59)	0.07	(0.00;0.18)	Pancreas	14	1.38	(0.76;2.32)	0.03	(−0.01;0.08)	2010
Upper aer.	31	1.04	(0.70;1.47)	0.02	(−0.10;0.18)	Oesophagus	22	**1.91**	(1.20;2.89)	0.41	(0.14;0.80)	Nose	6	1.67	(0.61;3.63)	0.32	(−0.10;1.16)	1380

Abbreviations: obs = observed number of cases; CI = confidence interval; SIR = standardised incidence ratio; PAF = population attributable fraction. Connective tis. = Connective tissue; Endocrine gl. = Endocrine glands; Hodgkin's dis. = Hodgkin's disease; Nervous sys. = Nervous system; Non-Hodgkin l. = Non-Hodgkin lymphoma; Upper aer. = Upper aerodigestive tract; Other male/fem. gen. = Other and unspecified male/female genital organs; Skin = Skin, non-squamous cell; Small int. = Small intestine; Thyroid gl. = Thyroid gland. Bold type represents significance at the 5% confidence level, underlined SIRs were significant after correcting for multiple testing (Benjamini–Hochberg method).

* Number of women exposed to the risk factor, i.e. number of women with an affected husband.

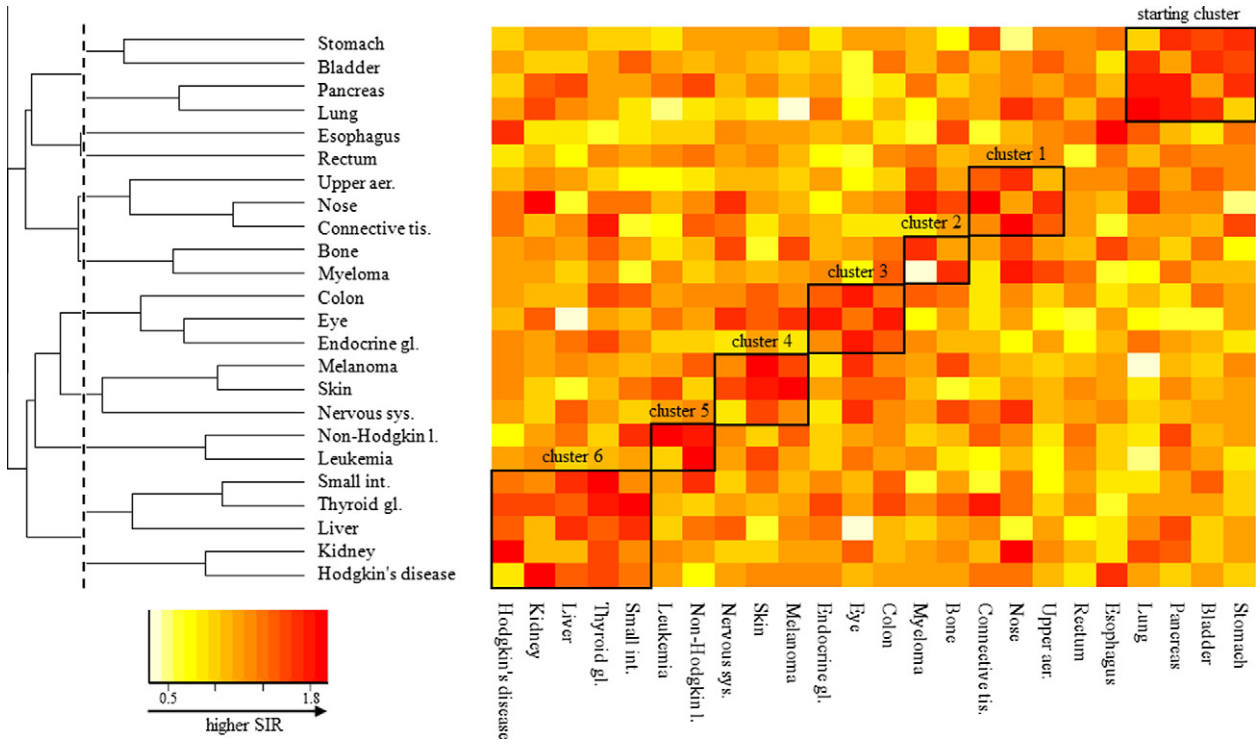

Fig. 1 – Clustering of cancer types in spouses. Dendrogram and heatmap are based on a distance matrix between any non-sex-specific cancer type, which relies on SIRs and displays the aggregation of cancer due to adult environmental exposures shared by spouses. The dashed line represents the cut-point for similarity based on the aggregation of stomach, bladder, pancreas and lung cancer.

would reduce the degree of environmental sharing. In addition the national registry does not include information on dietary habits, tobacco use and lifestyle aspects. The following discussion focuses on significant findings after controlling for multiple testing. The consistency of the observed results, for example the expected cluster of lung, stomach, pancreas and bladder cancers and the association of colon and eye cancer (SIR 1.84 for colon cancer in husbands of women with eye cancer and SIR 1.87 for eye cancer in wives of men affected with colon cancer) that was also replicated in the cluster analysis, adds confidence to our data. However, the reader should keep in mind that some associations were probably observed by chance. In order to keep the number of comparisons small, we used broad categories of cancer; however the definition of less broad categories may permit us to identify more specific etiological factors. This analysis could be carried out in the future.

Our findings are in broad agreement with previous studies showing only moderate spousal concordance for cancer occurrence.[14,10,25,26] Shared lifestyles including smoking and drinking habits as well as human papilloma virus infection (HPV) might be associated with an excess of cancer incidence amongst spouses. We observed significantly an increased risk for smoking-related cancers such as lung, upper aerodigestive tract and oesophageal cancers. amongst discordant types, HPV infection and smoking certainly contribute to the observed association between upper aerodigestive tract and cervical cancers.[27–29] The association of melanoma and skin cancers for wives might be related to frequent UV exposure shared by partners in their adulthood. In a previous publication the authors found an increased risk only for melanoma patients whose spouse was diagnosed before the age of 50 years and they did not observe any association for skin cancer.[11] Although cumulative exposure to UV radiation is an established risk factor for skin cancer including melanoma,[30,31] its effect might be more related to exposures during childhood and adolescence. Another interesting finding was the significantly increased risk of colon cancer for husbands of affected wives with eye cancer and vice versa. To our knowledge this association has not been reported before and might provide some hints to the yet unknown etiological factors. The association between eye and colon cancer was also supported by the heatmap, which incorporated the site "endocrine glands" to the cluster.

We calculated PAFs to quantify the burden of the disease attributable to having a spouse affected by cancer. The low SIRs and small exposure prevalences translated into PAFs under 1.5%. Consequently, shared lifestyle amongst spouses seems to explain only a small proportion of familial cancer.

At this point we would also like to emphasise, that even though the risk of many cancers is not significantly increased for spouses, environmental causes cannot be excluded. The environmental sharing of family members might be different during childhood and adulthood. Our data is in line with immigrant studies showing that the first generation of immigrants follows a cancer pattern similar to the country of origin. Swedish data have shown that the cancer incidence in the second generation born in Sweden agrees with the

incidence in the general Swedish population.[17,32,33] These findings suggest that the first two decades of life may be the most vulnerable period for carcinogenesis.

Based on the analysis of all non-sex-specific concordant and discordant types, we calculated a distance matrix displaying clusters of cancers with elevated risks. The advantage of this approach is that rather than exploring cancer sites one by one (i.e. in a one-dimensional way), we comprehensively summarise the SIRs for any cancer type at once (i.e. in a multidimensional way). The generated etiological map may help to establish the yet unknown common risk factors for cancer. For this purpose the resulting aggregation of lung, stomach, pancreas and bladder cancer, which share smoking as a risk factor, was used as a cut-point to identify the remaining clusters. In the following we discuss some of the clusters in more detail.

One of the clusters that we identified included melanoma, nervous system and skin cancers. Ionising radiation is a well-recognised factor associated with cancer of the nervous system.[34] Whilst there is some evidence for other environmental risk factors such as mobile phones or electromagnetic fields,[35–38] epidemiological results are not conclusive.[39–41] UV radiation, much weaker than ionising radiation, has been recognised as a factor associated with skin cancer and melanoma.[30,31] Although UV radiation has not been connected to brain cancer, another study from the Swedish Family-Cancer Database reported significantly increased risks for skin cancer in spouses of primary brain tumour patients. The authors argued that even signals with a much shorter range such as radio signals have been linked to increased risk for brain tumours.[42]

Leukaemia and non-Hodgkin's lymphoma also aggregated in spouses in a cluster with significantly increased risk for husbands with affected wives and the other way round (SIR 1.31 for non-Hodgkin's lymphoma in husbands of women with leukaemia, SIR 1.28 for leukaemia in wives of men with non-Hodgkin's lymphoma, data not shown here). Both cancers are haematolymphoproliferative disorders with non-Hodgkin's lymphoma as the most common subgroup. Risk factors for non-Hodgkin's lymphoma are immunodeficiencies caused by HIV and other infectious agents, such as the human herpesvirus 8 and Epstein–Barr virus as well as cigarette smoking.[43,44] There is also evidence for association between non-Hodgkin's lymphoma and UV radiation causing immune impairment[45,46] (references within). Further potential factors are exposure to pesticides, herbicides or organic solvents.[47] The development of leukaemia has been associated with several environmental risk factors including smoking, exposure to viruses, ionising radiation, herbicides and pesticides.[48] Common virus infections as well as smoking possibly play a role in the observed association between leukaemia and non-Hodgkin's lymphoma.

Another cluster included myeloma and primary bone cancer. Ionising radiation, repeated infections, cigarette smoking, several immune-related diseases, farming and occupational exposure to benzene have been identified as factors in the development of myeloma.[49] There is also an increased incidence of multiple myeloma in persons with rheumatoid arthritis or obesity[50] (references within). The most common types of primary bone cancer are osteosarcoma, chondrosarcoma and Ewing sarcoma and are more common amongst young people. Osteosarcoma is the most common malignant tumour of the bone, with a peak incidence during the adolescent growth spurt, but there is also a significant second peak in the seventh and eighth decades of life. Chondrosarcoma usually affects people over age 40 years, arising from the central portions of the skeleton. Risk factors for primary bone cancer are ionising radiation, Paget's disease and retinoblastoma.[51] Exposure to ionising radiation may be one of the linking environmental factors in this cluster.

In conclusion, our findings show small increased risks for cancer amongst spouses and suggest that only strong environmental risk factors such as smoking modifies cancer risk in adulthood. In general, the lifestyle shared by spouses seems to play a minor role in cancer development. The proposed etiological map based on a comprehensive summary of 24 cancer types identifies some clusters – for example, non-Hodgkin lymphoma and leukaemia, bone cancer and myeloma – that are likely related to exposure to yet unidentified environmental risk factors during adulthood.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.06.125.

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