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Determining the familial risk distribution of colorectal cancer: A data mining approach

Short title: Familial risk of colorectal cancer

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DISCLOSURE

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ABSTRACT

This study was aimed to characterize distribution of colorectal cancer risk using family history of cancers by data mining. Family histories for 10,066 colorectal cancer cases recruited to population cancer registries of the Colon Cancer Family Registry were analyzed using a data mining framework. A novel index was developed to quantify familial cancer aggregation. Artificial neural network was used to identify distinct categories of familial risk. Standardized incidence ratios (SIRs) and corresponding 95% confidence intervals (CIs) for colorectal cancer were calculated for each category. We identified five major, and sixty-six minor categories of familial risk for developing colorectal cancer. The distribution the major risk categories were: (i) 7% of families (SIR=7.11; 95%CI=6.65-7.59) had a strong family history of colorectal cancer; (ii) 13% of families (SIR=2.94; 95%CI=2.78-3.10) had moderate family history of colorectal cancer; (iii) 11% of families (SIR=1.23; 95%CI=1.12-1.36) had strong family history of breast cancer and weak family history of colorectal cancer; (iv) 9% of families (SIR=1.06; 95% CI=0.96-1.18) had strong family history of prostate cancer and weak family history of colorectal cancer; and (v) 60% of families (SIR=0.61; 95%CI=0.57-0.65) had weak family history of all cancers. There is a wide variation of colorectal cancer risk that can be categorized defined by family history of cancer, with a strong gradient of colorectal cancer risk between the highest and lowest risk categories. Risk of colorectal cancer for people with the highest risk category of family history (7% of the population) was 12-times that for people in the lowest risk category (60%) of the population. Data mining was proven an effective approach for gaining insight to the underlying cancer aggregation patterns and for categorizing familial risk of colorectal cancer.

INTRODUCTION

Risk of colorectal cancer is strongly associated with family history of colorectal cancer. First-degree relatives of colorectal cancer cases have, on average, an approximate two-fold risk of the disease compared with those without a family history [1, 2]. Knowledge of this risk factor, has led to the development of guidelines for colorectal cancer screening based on family history and research to identify the genetic factors that contribute to this familial risk. Hereditary cancer syndromes, such as Lynch syndrome and familial adenomatous polyposis, for which underlying genetic mutations have been identified, are major achievements, yet account for the minority of this familial aggregation [3]. A more comprehensive assessment of how familial aggregation of cancer affects colorectal cancer risk, and the distribution of this risk, would provide the basis for formulating new genetic and genomic research, and development of improved clinical management of colorectal cancer families, including refining targeted genetic and cancer screening recommendations. The distribution of familial risk was first analyzed by Fain and Goldgar using a non-parametric test applying to breast cancer family history data [4].

Most studies investigating associations between family history and risk of colorectal cancer have limited their analysis of family history to first-degree relatives only [5-10] with only a few that included up to third-degree relatives [1, 11]. Most have not considered family history of cancers other than colorectal and have used simple counts of cancers without considering the size of the family or degree of relationship. A limitation of this approach is that the underlying association between the constellation of affected relatives and the patterns of aggregation of cancer in relatives is not taken into account. A more comprehensive approach is to address the question:

"What is a person's risk of colorectal cancer if *l* of this person's *x* first-degree relatives had cancer *a, b, c* …, and *m* of this person's *y* second-degree relatives had cancer *a, b, c,* …, and *n* of this persons's *z* third-degree relatives had cancer *a, b, c,* ….?"

To the best of our knowledge, no study has reported the distribution of risk of colorectal cancer, taking into consideration both the underlying association between the patterns of affected relatives (constellations) and the spectrum of co-aggregating cancers (aggregations). We have attempted to fill this gap by conducting a novel data mining approach to identify categories of familial risk by clustering constellations and aggregations simultaneously.

MATERIALS AND METHODS

Study Sample

We studied population-based colorectal cancer families recruited to the Colon Cancer Family Registry [12]. Detail description of recruitment can be found at http://coloncfr.org/. For this analysis, we studied the families that were recruited through recently diagnosed invasive colorectal cancer cases (population-based probands) from state or regional population cancer registries in the USA (Washington, California, Arizona, Minnesota, Colorado, New Hampshire, North Carolina, and Hawaii), Australia (Victoria) and Canada (Ontario) between 1997 and 2007. Population-based probands were recruited regardless of having a family history of cancer. Written informed consent was obtained from all study participants, and the study protocol was approved by the institutional research ethics review board at each study center.

Data Collection

Information on demographics, personal characteristics, personal and family history of cancer, cancer-screening history, and history of polyps, polypectomy, and other surgeries was obtained by questionnaires from all probands and participating relatives. Cancer histories were also cross checked across multiple relatives from within the same family, not just the probands. Participants were followed up approximately every five years after baseline to update this information. The present study was based on all available baseline and follow-up data. Reported cancer diagnoses and age at diagnosis were confirmed, where possible, using pathology reports, medical records, cancer registry reports, and death certificates. Blood samples and permission to access tumor tissue were requested from all participants.

Mismatch repair (MMR) gene mutation testing

Testing for germline mutations in *MLH1, MSH2, MSH6* and *PMS2* was performed for all population-based probands who had a colorectal cancer displaying MMR deficiency as evidenced by either tumor microsatellite instability and/or lack of MMR protein expression by immunohistochemistry. Details of germline testing methods have been described elsewhere [13]. A pathogenic mutation was defined as a variant that was predicted to result in a stop codon, a frameshift mutation, a large duplication or deletion, or a missense mutation in the coding region or splice site previously reported within the scientific literature and databases to be pathogenic (InSiGHT database; http://insight-group.org/variants/classifications/). The relatives of probands with a pathogenic MMR germline mutation, who provided a blood sample, underwent testing for the specific mutation identified in the proband.

Definitions

Self-organizing map [14] is a method for projecting high-dimensional data onto low-dimensional output display. A *node* corresponds to a group of families with similar familial aggregation vectors and is determined using a self-organizing map. *K-means* [15] is a technique for partitioning data into optimal groups. A *cluster* is a grouping of nodes on the self-organizing map detected by k-means. A *codebook vector* refers to the weight vector of each node for the self-organizing map. A *prototype vector* is used to describe the mean weight vector for a cluster computed by k-means.

Statistical Analysis

Data mining framework

To analyze family history , we used data mining [16] to reveal patterns of familial aggregation that can be used to estimate colorectal cancer risk of an individual based on their family history of cancers. Every family was represented by a vector modeling family history of cancer. These vectors became the inputs to the clustering algorithms, including the self-organizing map [14] and k-means [15], to identify nodes and clusters. Finally, the risk of colorectal cancer was estimated for each detected nodes and cluster (see Supplementary Figure 1).

(1) Familial aggregation

Family history of each cancer type was transformed into familial aggregation index that encapsulated the aggregation in each family with the key properties that family history of cancer for a person is stronger the larger numbers of relatives with cancer and the closer the genetic

relationship they have to these affected relatives. To this end, the vector of familial aggregation of all cancers for each family based on the familial relationship to the proband, was calculated as follows:

$$\text{fam}_x = (F_Agg_{c_1} , F_Agg_{c_2} , \dots , F_Agg_{c_n}), \quad \text{for cancer } c_1 \text{ to } c_n$$

where $F_Agg_{c_i}$ is a familial aggregation index defined as:

$$F_Agg_{c_i} = \frac{\#FDR_{c_i} \times 4 + \#SDR_{c_i} \times 2 + \#TDR_{c_i} \times 1}{\#FDR \times 4 + \#SDR \times 2 + \#TDR \times 1}$$

with

$\#FDR$, $\#SDR$, $\#TDR$ as the numbers of first-, second- and third-degree relatives the proband has, and

$\#FDR_{c_i}$, $\#SDR_{c_i}$, $\#TDR_{c_i}$ as the numbers of first-, second- and third-degree relatives of the proband being affected by cancer c_i.

(2) Cluster detection

First, the self-organizing map [14] (a non-parametric clustering algorithm from the artificial neural network [17] discipline) was applied to group families with similar family history as defined by their familial aggregation index into nodes so that neighboring nodes are more similar than distant ones. Second, k-means [15] was used to identify global characteristics of familial aggregation by partitioning the nodes into larger clusters so that similarity within cluster and difference between clusters were maximized.

A 6×12 (72 nodes) self-organizing map was used. The number of nodes was initially set to $5\sqrt{n}$, where n was the number of families, and the vertical and horizontal dimension was defined by the ratio of the two largest eigenvalues of the dataset. The final map size used was chosen by scaling up or down the reference map to achieve maximum map resolution within computational constraints [18].

To find a global perspective for the familial aggregation, families grouped by nodes on the self-organizing map were further clustered using k-means, where k is the number of clusters to be found. K-means is a partitioning clustering algorithm useful for providing groupings with explicit cluster boundaries [15]. All cluster detection tasks were done using the scientific programming package Matlab R2012a [19]. Technical details of the cluster detection step, including (1) clustering families using the self-organizing map, (2) partitioning self-organizing map using k-means, and (3) distance measure for measuring similarity of familial aggregation, are described in the Appendix A, B and C, respectively.

(3) Epidemiologic analysis

To determine the degree of colorectal cancer risk for family members of each node and cluster compared with the general population, we estimated the standardized incidence ratio (SIR) by dividing the numbers of colorectal cancers observed in all family members (excluding the proband) of each node and cluster by the expected numbers [20]. The expected numbers of colorectal cancers for each node and cluster were calculated by multiplying the age-, sex-, and country-specific incidence for the general population with the corresponding observation time (i.e. age) of the family members. Age- and sex-specific cancer incidences for each country in 1988-1992 were obtained from the Cancer Incidence in Five Continents [21]. The corresponding

95% confidence intervals (CIs) were calculated by taking into account of familial correlation of cancer risk between relatives using the Jackknife method [22].

To deal with missing age(s) at diagnosis of cancer for affected relatives, we assumed the median age at diagnosis for each cancer in the general population obtained from Surveillance, epidemiology and End Results Cancer Statistics Review [23]. Unaffected relatives for whom no information on age was available were censored at birth and therefore did not contribute to the analysis. All epidemiologic analysis was done using Stata 11.0 [24].

We conducted a sensitivity analysis to assess the role of an inherited cancer risk syndrome on familial clustering and SIR estimation by excluding the 201 families known to be carrying a DNA mismatch repair gene mutation (Lynch syndrome families). We conducted a sensitivity analysis to assess the role of family history to third-degree relatives by restricting analysis to only first- and second-degree relatives.

RESULTS

Of the 10,407 families identified from population-based resources of the Colon Cancer Family Registry, 341 families (3%) were excluded because of having less than four family members. The remaining 10,066 families that contained 181,555 individuals (90,188 women) were included. On average, each family had 7 first-degree relatives, 9 second-degree relatives and 5 third-degree relatives (Table 1). We identified sixty-six minor clusters of familial risk for developing colorectal cancer (Figure 1). There are 5 major clusters corresponding to an optimal partition capturing the most representative family history patterns associated with various

degrees of risk for developing colorectal cancer (Supplementary Figure 2). Demographic characteristics of each cluster are summarized in Table 2.

Identification of the familial risk

Familial risk of colorectal cancer identified for the Colon Cancer Family Registry families is depicted in Supplementary Figure 3. There was a moderate variation in colorectal cancer risk across nodes within each cluster (Figure 1) and a wide variation in colorectal cancer risk across clusters in terms of both the type and strength of aggregation of extracolonic cancers and the strength of aggregation of colorectal cancer (Figure 2).

Familial risk for each cluster

Members of families with the strongest aggregation of colorectal cancer had the highest risk of the disease (Cluster 5 in Figure 2), with an average seven-fold increased risk of colorectal cancer compared with the general population (SIR = 7.11; 95% CI = 6.65 to 7.59). Within this cluster, the increased risk for colorectal cancer ranged from 3.64 to 10.08 (between the 8 nodes). This cluster comprised 742 families, which is 7% of all families, and the median age of disease onset is 67 (inter-quartile range 52-72) years. Members of families with the second highest aggregation of colorectal cancer (Cluster 4 in Figure 2), had an average three-fold increased risk of colorectal cancer (SIR = 2.94; 95% CI = 2.78 to 3.10). Within this cluster, the increased risk for colorectal cancer ranged from 1.64 to 4.22 (between the 13 nodes). This cluster comprised 1,353 families, which is 13% of all families, and the median age of disease onset is 69 (inter-quartile range 52-72) years. In contrast, colorectal cancer risk was the lowest for members of families with weak aggregation of colorectal cancer (Cluster 1 in Figure 2). They had an average

risk of colorectal cancer 40% lower than the general population (SIR = 0.61; 95% CI = 0.57 to 0.65). Within this cluster, the increased risk for colorectal cancer ranged from 0.1 to 2.34 (between the 24 nodes). This cluster comprised 5,969 families, which is 60% of all families, and the median age of disease onset is 70 (inter-quartile range 56-72) years.

Members of families with a strong aggregation of breast cancer and weak aggregation of colorectal cancer (Cluster 3 in Figure 2) had a modest increased risk of colorectal cancer (SIR = 1.23; 95% CI = 1.12 to 1.36) i.e., familial aggregation of breast cancer was a risk factor for colorectal cancer. Within this cluster, the increased risk for colorectal cancer ranged from 0.24 to 3.89 (between the 10 nodes). This cluster comprised 1,087 families, which is 11% of all families, and the median age of disease onset is 71 (inter-quartile range 61-72) years. Members of families with a strong aggregation of prostate cancer and weak aggregation of colorectal cancer (Cluster 2 in Figure 2) had no increased risk of colorectal cancer (SIR = 1.06; 95% CI = 0.96 to 1.18) i.e., familial aggregation of prostate cancer was not a risk factor for colorectal cancer. Within this cluster, the increased risk for colorectal cancer ranged from 0.27 to 2.93 (between the 11 nodes). This cluster comprised 915 families, which is 9% of all families, and the median age of disease onset is 71 (inter-quartile range 43-74) years.

Extracolonic cancers co-aggregated with colorectal cancer in all five clusters but the aggregations were all weak and no particular cancer appeared to be a risk factor for colorectal cancer except in Cluster 3. Averaged across all nodes in all clusters weighted by the number of families in each node, the SIR was 1.59 (95% CI = 1.54 to 1.65).

Distribution of familial risks by clusters

Figure 3A shows the distribution of SIRs for colorectal cancer for all family members within each node for each of the five clusters. Familial risk distributions were similarly right skewed for Clusters 1, 2 and 3): about 90% of families in Cluster 1 had a lower risk of colorectal cancer than the general population; about 80% in Cluster 2; and about 60% in Cluster 3. When we compared the familial risks (expressed by SIRs) between different clusters, there was a strong gradient between them (Figure 3B). The ratio of the SIRs between the highest risk category of family history (Cluster 5) and the lowest risk category (Cluster 1), was 11.67. When combined across all nodes in all clusters, i.e. all families, the overall distribution of familial risks in the whole study sample was right skewed with a long tail (Figure 4).

Sensitivity analyses

There were 201 (2%) families in which at least one family member was identified as having a MMR gene mutation (Lynch syndrome). Excluding the Lynch syndrome families made no substantial difference to the findings in terms of self-organizing map patterns, distributions of aggregating cancers in families, age at diagnosis, or SIR of colorectal cancer in any cluster (Supplementary Figure 4). The distribution of familial clusters for Lynch syndrome families, median age at diagnosis and SIR of colorectal cancer for each cluster are shown in Supplementary Table 1. Similarly, excluding all third-degree relatives made no substantial difference (detail data not shown).

DISCUSSION

In this study, we identified patterns of familial aggregation and simultaneously assessed risk of colorectal cancer for these familial aggregation patterns, instead of estimating risk only based on numbers of affected relatives and degree of relatedness as in previous studies [25-28]. We used a novel data mining approach, which facilitated the clustering of both constellation patterns and familial cancer aggregation. The multivariable nature of this approach is particularly relevant for examining risk where cancers at multiple organ sites can co-aggregate within the family.

We found that the overall distribution of the familial risks of colorectal cancer across the whole study sample (all of whom had at least one relative with colorectal cancer, i.e. the proband) to be right skewed (Figure 4). This is consistent with the description of familial risks of people in the general population by Hopper [29] (see Figure 2 in [29]): under the assumption of a multiplicative polygenic risk model, the distribution of familial risks for colorectal cancer for the general population (and in our case, families with at least one colorectal cancer) is skewed with a long tail, and the mode of the familial risk is substantially below the population average of 5% risk. Moreover, a trend parallel to Hopper's description was clearly observed in our cluster familial risk distributions. The average familial risk distributions spread further to the right as more close relatives are affected [29, 30]. Starting from the lowest risk category (Cluster 1), as the average familial risk increases (Cluster 2 and 3), the distribution of the familial risks moves to the right (Cluster 4 and 5). We, therefore, provide empirical evidence for the existence of a wide variation of familial risks (even within a set of families ascertained because of a colorectal cancer case), and a strong gradient of colorectal cancer risk between the highest and lowest risk groups for colorectal cancer. We also found that the types and aggregation of extracolonic

cancers and strength of the aggregation of colorectal cancer in a family might explain this wide variation of familial risks of colorectal cancer.

This study has some limitations. The clustering results of the self-organizing map will not be identical every time it is run though they were very similar consistently. This is a common issue for neural network models and optimization problems in general. However, it is not a major concern here because the focus is in identifying a small finite set of representative prototypes (i.e. the familial risk categories) by minimizing the quantization error of the neural network model. These prototypes are formed as averages of the data within a cluster. Variations of these averages are insignificant when the number of training data is sufficiently large, as in our case.

The contribution this study could make to the field is two-fold. First, the findings about the familial risk distribution will serve as empirical evidence supporting existing familial risk models confirming that, for colorectal cancer, there exist a wide variation of familial risks, and a very strong risk gradient between the highest and lowest risk groups [29, 31]. Second, the data mining approach will advance current familial studies which are limited to univariable analysis to addressing the multivariable question, relevant to the studies of other familial cancer syndromes.

In conclusion, our data mining approach showed a wide variation of familial colorectal cancer risk and a strong risk gradient between the highest risk and lowest risk families. The types and aggregation of extracolonic cancers and strength of the aggregation of colorectal cancer in a family might explain this wide variation of familial risks. A family history of colorectal cancer with a broad spectrum of co-aggregating cancers could significantly elevate the risk of colorectal cancer; but co-aggregating extracolonic cancers may not influence risk of colorectal cancer when

the familial aggregation of colorectal cancer is not strong. Data mining was proven an effective approach for gaining insight to the underlying cancer aggregation patterns and for categorizing familial risk of colorectal cancer.

REFERENCES

1. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA (2010) Population-Based Family History-Specific Risks for Colorectal Cancer: A Constellation Approach. Gastroenterology 138(3): 877-85

2. Baglietto L, Jenkins MA, Severi G, et al. (2006) Measures of familial aggregation depend on definition of family history: meta-analysis for colorectal cancer. J Clin Epidemiol 59(2): 114-24

3. Al-Sukhni W, Aronson M, Gallinger S (2008) Hereditary colorectal cancer syndromes: familial adenomatous polyposis and lynch syndrome. Surg Clin North Am 88(4): 819-44, vii

4. Fain PR, Goldgar DE (1986) A nonparametric test of heterogeneity of family risk. Genetic epidemiology Supplement 1: 61-6

5. Negri E, Braga C, La Vecchia C, et al. (1998) Family history of cancer and risk of colorectal cancer in Italy. Br J Cancer 77(1): 174-9

6. Johns LE, Houlston RS (2001) A systematic review and meta-analysis of familial colorectal cancer risk. Am J Gastroenterol 96(10): 2992-3003

7. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC (1994) A prospective study of family history and the risk of colorectal cancer. N Engl J Med 331(25): 1669-74

8. Goldgar DE, Easton DF, Cannon-Albright LA, Skolnick MH (1994) Systematic population-based assessment of cancer risk in first-degree relatives of cancer probands. Journal of the National Cancer Institute 86(21): 1600-8

9. Ahsan H, Neugut AI, Garbowski GC, et al. (1998) Family history of colorectal adenomatous polyps and increased risk for colorectal cancer. Ann Intern Med 128(11): 900-5

10. Winawer SJ, Zauber AG, Gerdes H, et al. (1996) Risk of colorectal cancer in the families of patients with adenomatous polyps. National Polyp Study Workgroup. N Engl J Med 334(2): 82-7

11. Slattery ML, Kerber RA (1994) Family history of cancer and colon cancer risk: the Utah Population Database. J Natl Cancer Inst 86(21): 1618-26

12. Newcomb PA, Baron J, Cotterchio M, et al. (2007) Colon Cancer Family Registry: an international resource for studies of the genetic epidemiology of colon cancer. Cancer Epidemiol Biomarkers Prev 16(11): 2331-43

13. Win AK, Lindor NM, Young JP, et al. (2012) Risks of primary extracolonic cancers following colorectal cancer in Lynch syndrome. J Natl Cancer Inst 104(18): 1363-72
14. Kohonen T (2001) Self-organizing maps. 3rd ed. Berlin ; New York, Springer
15. Jain AK, Murty MN, Flynn PJ (1999) Data clustering: a review. ACM Comput Surv 31(3): 264-323
16. Hastie T, Tibshirani R, Friedman JH (2009) The elements of statistical learning : data mining, inference, and prediction. 2nd ed. New York, Springer
17. Haykin SS (2009) Neural networks and learning machines. 3rd ed. New York, Prentice Hall
18. Vesanto J, Himberg J, Alhoniemi E, Parhankangas J (2000) SOM toolbox for Matlab. Tech Rep Laboratory of Computer and Information Science, Helsinki University of Technology:
19. The MathWorks I MATLAB version 7.10.0. . In: Natick, Massachusetts.; 2010.,
20. Breslow NE, Day NE (1987) Statistical methods in cancer research. Volume II--The design and analysis of cohort studies. IARC scientific publications (82): 1-406
21. Parkin DM WS, Ferlay J, Storm H. (1997) Cancer incidence in five continents. Volume VII. IARC scientific publications (143): i-xxxiv, 1-1240
22. Gould W (1995) Jackknife estimation. Stata Technical Bulletin (4): 25-9
23. Ries L, Eisner M, Kosary C, et al. SEER Cancer Statistics Review, 1975-2000. Bethesda, MD, 2003., National Cancer Institute;,
24. StataCorp. Stata Statistical Software: Release 11. In: College Station, TX: StataCorp LP; 2009.,
25. Taylor DP, Burt RW, Williams MS, Haug PJ, Cannon-Albright LA (2010) Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology 138(3): 877-85
26. Kerber RA, O'Brien E (2005) A cohort study of cancer risk in relation to family histories of cancer in the Utah population database. Cancer 103(9): 1906-15
27. Teerlink CC, Albright FS, Lins L, Cannon-Albright LA (2012) A comprehensive survey of cancer risks in extended families. Genet Med 14(1): 107-14
28. Andrieu N, Launoy G, Guillois R, Ory-Paoletti C, Gignoux M (2004) Estimation of the familial relative risk of cancer by site from a French population based family study on colorectal cancer (CCREF study). Gut 53(9): 1322-8

29. Hopper JL (2011) Disease-specific prospective family study cohorts enriched for familial risk. Epidemiol Perspect Innov 8(1): 2

30. Win AK, Ait Ouakrim D, Jenkins MA (2014) Risk profiling: familial colorectal cancer. Cancer Forum 38(1): 15-25

31. Hopper JL, Carlin JB (1992) Familial Aggregation of a Disease Consequent upon Correlation between Relatives in a Risk Factor Measured on a Continuous Scale. Am J Epidemiol 136(9): 1138-47

Table 1: Baseline characteristics of population-based families from the Colon Cancer Family Registry

Characteristics	**Number**
No. of families	10,066
No. of persons	181,555
Canada	60,875 (34%)
Australia	34,669 (19%)
USA	86,011 (47%)
Male : Female	1 : 1.01
Age (median)	57
Cancers	
Colorectal cancer	6,808
Endometrial cancer	858
Stomach cancer	1,526
Small bowel cancer	46
Hepatobiliary tract cancer	754
Pancreatic cancer	680
Renal cancer	478
Ureter cancer	32
Bladder cancer	504
Brain cancer	806
Cervical cancer	586
Ovarian cancer	610
Breast cancer	3,841
Prostate cancer	2,470

Table 2: Demographic characteristics of five clusters

Cluster	No of families	No of persons	Male : Female	Age (years) median (inter-quartile range)
1	5,969 (59%)	96,326	1 : 1.02	56 (40-72)
2	915 (9%)	19,544	1 : 1.02	59 (43-74)
3	1,087 (11%)	19,916	1 : 0.95	59 (43-73)
4	1,353 (13%)	33,938	1 : 1.01	57 (40-73)
5	742 (7%)	11,831	1 : 0.99	58 (42-72)

Figure Legends

Figure 1. Familial risks for population-based colorectal cancer families from the Colon Cancer Family Registry. The number in the right top corner represents the standardized incidence ratio of colorectal cancer. Node without a bar chart in the diagram is an empty node with no families mapped to it.

Figure 2. Familial risk of colorectal cancer by each cluster. SIR, standardized incidence ratio of colorectal cancer; ageDX, age at diagnosis of colorectal cancer (years).

Figure 3.

(A) Distribution of familial risk of colorectal cancer by family clusters (expressed by the standardized incidence ratios (SIRs)). The *normalized frequency*, corresponding to the height of each bar, indicates the percentage of families with the same colorectal cancer risk.

(B) Standardized incidence ratios and their 95% confidence intervals for each family cluster. The *dot points* represent the estimates of standardized incidence ratio (SIR) and the *vertical lines* represent 95% confidence intervals.

Figure 4. Mapping between familial risk distribution and cancer aggregation patterns. SIR, standardized incidence ratio of colorectal cancer; ageDX, age at diagnosis of colorectal cancer (years).

Appendix A: Clustering families using self-organizing map

Let $\mathbf{x}_i \in R^N$ $(1 \le i \le M)$ be the familial aggregation vector of the i^{th} family in the dataset, where N is the number of cancer categories included in the analysis, and M is the total number of families. The self-organizing map consists of a regular grid of nodes. Each node is associated with an N-dimensional codebook vector. Let $\mathbf{m}_j = [m_{jn} | 1 \le n \le N]$ $(1 \le j \le G)$ be the codebook vector of the j^{th} node on the map. The training algorithm for forming the *familial aggregation space* is given as follows:

1: Present an input vector $\mathbf{x}_i$ for training at random.

2: Find the winning node s on the map with the vector $\mathbf{m}_s$ which is closest to $\mathbf{x}_i$ such that

$$\left\|\mathbf{x}_i - \mathbf{m}_s\right\| = \min_j \left\|\mathbf{x}_i - \mathbf{m}_j\right\|$$

3: After the winning node *s* is selected, update the weight of every node in the neighbourhood of node *s* by

$$\mathbf{m}_t^{new} = \mathbf{m}_t^{old} + \alpha(t)(\mathbf{x}_i - \mathbf{m}_t^{old})$$

where $\alpha(t)$ is the gain term at time *t* ($0 \le \alpha(t) \le 1$) that decreases in time and converges to 0.

4: Increase the time stamp *t* and repeat the training process until it converges.

After the training process was completed, each input vector (i.e. family) was mapped to a grid node closest to it on the self-organizing map. A *familial aggregation space* was thus formed. This process corresponded to a projection of the multi-dimensional input vectors onto an orderly two-dimensional space where the proximity of the input vectors was preserved as faithfully as possible. Consequently, familial similarities, in terms of both the types of extracolonic cancers and the strength of the CRC aggregation were explicitly revealed by their locations and neighbourhood relationships on the map. For all families mapped to a node, a familial risk category, based on family history of cancer, was then revealed by retrieving the codebook vector correspond to a node on the self-organizing map.

Appendix B: Partitioning the self-organizing map using k-means

The k-means algorithm used for running on the *familial aggregation space* was as follow:

1: Select k nodes from the self-organizing map as initial cluster centers.

2: Form k clusters by assigning each node to its closest cluster center.

3: Re-compute the cluster centers as the means of all its cluster members.

4: Repeat the process from step 2 until the cluster centers no longer change.

K-means was run for different values of *k*, and we chose the optimal partition of the self-organizing map, validated by the Davies-Bouldin index [1], so that distances within clusters were minimized and distances between clusters were maximized. The Davies-Bouldin index minimizes the expression:

$$\frac{1}{C}\sum_{i=1}^{C} max_j \left(\frac{S_i + S_j}{M_{ij}}\right)$$

where C is the number of clusters, S_i is the dispersion of cluster i defined in terms of mean squared distance from the cluster center, and M_{ij} is the distance between the centers of cluster i and j [2]. Thus, the optimal partition implies that, by grouping families based on similarity of family history, a family is then more similar to any family belonging to the same cluster than with any other family in a different cluster.

Finally, *k* cluster-wide familial risk categories were revealed by finding the prototype vectors corresponding to the *k* cluster centers. A cluster-wide familial risk category characterizes each family of a cluster by summarizing the global characteristics of cancer aggregation of all families in that cluster. It is essentially the mean vector of all codebook vectors associated to a cluster.

Appendix C: Distance measure for similarity of familial aggregation

Central to every cluster algorithm is a metric for measuring distance (or similarity) between objects. Euclidean distance

$$\boldsymbol{d(x_1, x_2) = \sqrt{\|x_1\|^2 + \|x_2\|^2 - 2x_1' x_2}}$$

is the default distance measure for most clustering algorithm, including the Self-organizing map and k-means. One limitation of the Euclidean distance is that it does not discriminate features which are present in one vector but absent in another vector [3], making it incapable of recognizing similarity of familial aggregation in epidemiological sense. For example, we have 3 families (*a*, *b* and *c*) and each family is represented by a 4-dimensional familial aggregation vectors featuring 4 cancers:

$a = (0, \quad 0.1, \quad 0.1, \quad 0 \quad)$

$b = (0.1, \quad 0, \quad 0, \quad 0.1)$

$c = (0.1, \quad 0.2, \quad 0.2, \quad 0.1)$

There is no common aggregating cancer between family *a* and family *b*, but there are two common aggregating cancers between family *a* and family *c*. In terms of familial aggregation, families sharing no common aggregating cancers should not be considered similar. Therefore, family *a* should be more similar to family *c* than family *b*, but Euclidean distance delivers count-intuitive result, $d(a,b)=0.2$ and $d(a,c)=0.2$, indicating that family *a* is equally similar to family *b* and family *c*.

To overcome limitations of the Euclidean distance, we adopted the extended Jaccard distance [3] as an alternative.

$$\boldsymbol{d(x_1, x_2) = 1 - \frac{x_1' x_2}{\|x_1\|^2 + \|x_2\|^2 - x_1' x_2}}$$

It is bounded between 0 and 1 with 0 representing perfect match and 1 representing there is no similarity at all. The extended Jaccard distance overcomes limitation of the Euclidean distance by comparing features shared by both vectors against features present in just either one of the two vectors. As such, it will measure similarity of familial aggregation in a more epidemiological sensible manner, by comparing weights of aggregation cancers shared by two families against weights of cancers aggregating in just either one of two families, indicating that, $d(a,b)=1$ and $d(a,c)=0.5$, suggesting that family *a* is more similar to family *c* than family *b*.

Figure 1

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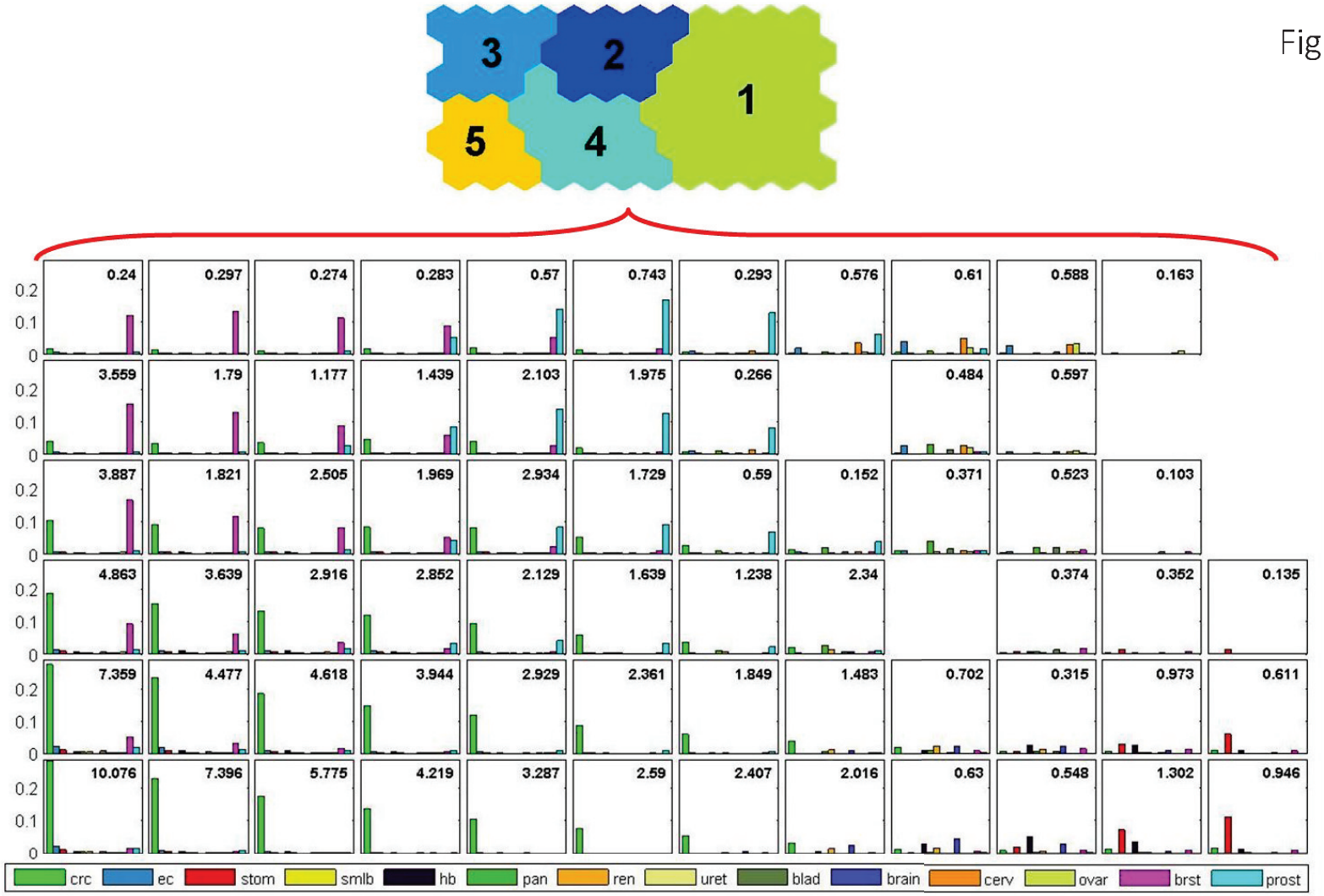


Figure 1

Figure 2

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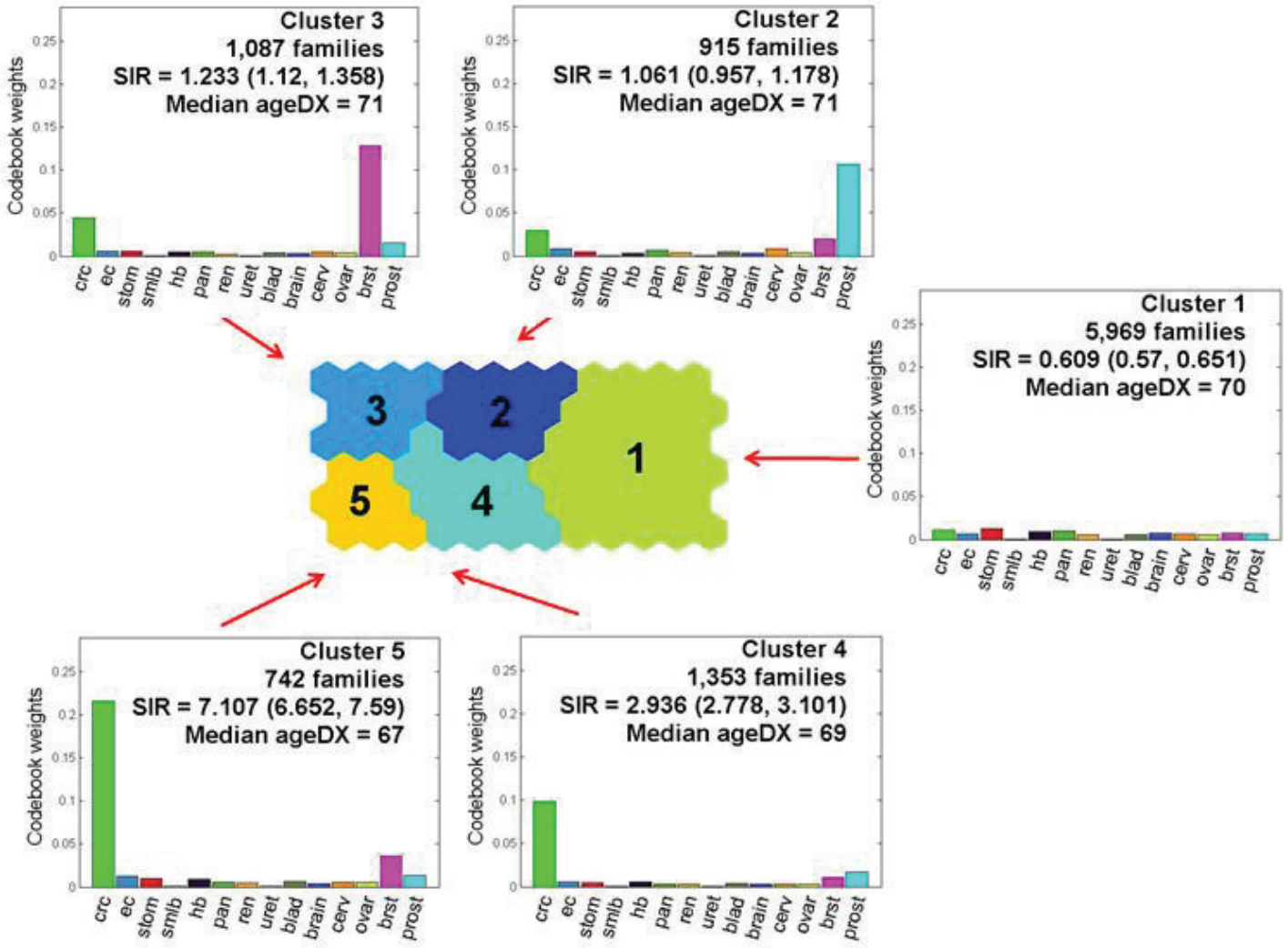


Figure 2

Figure 3

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Figure 3A

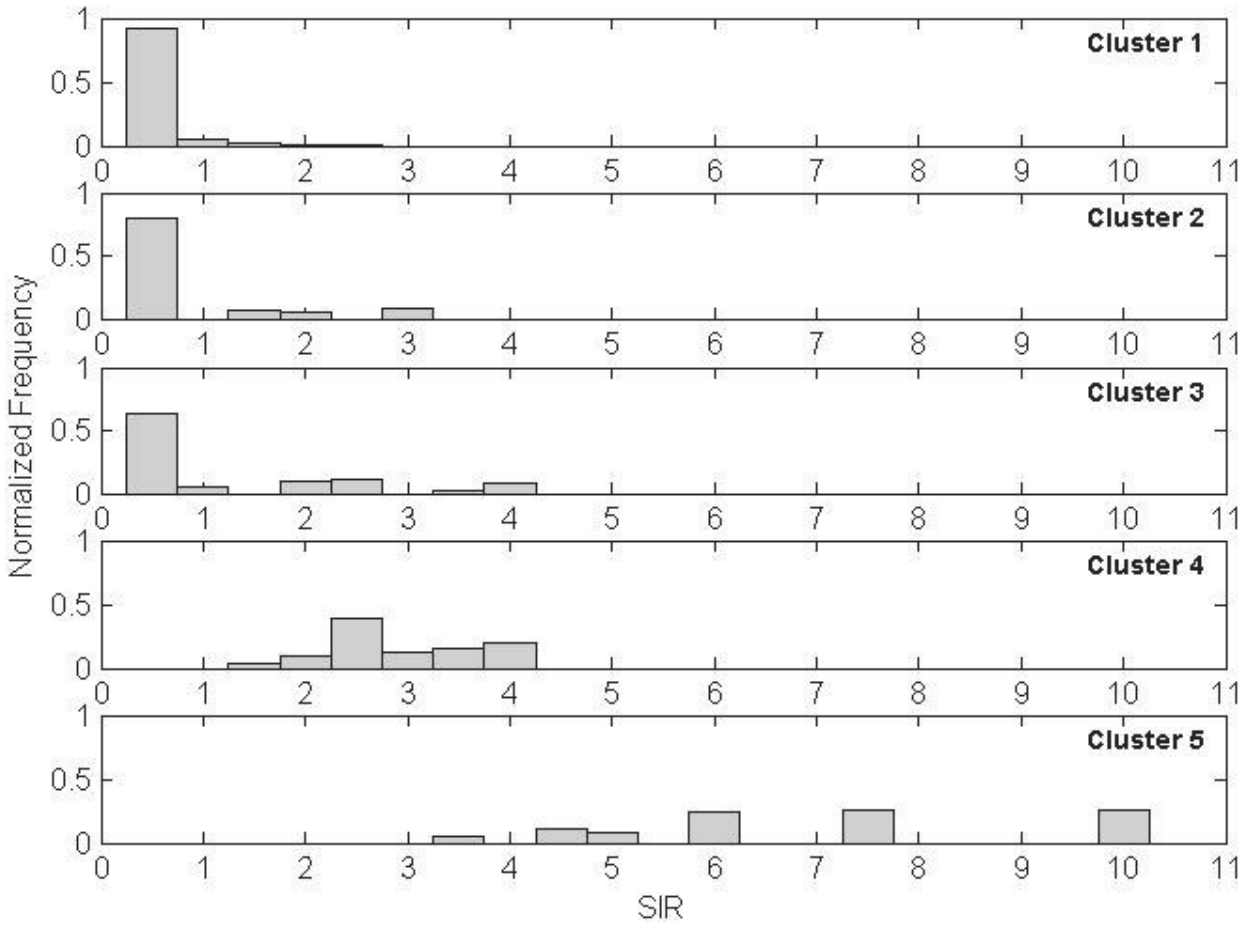


Figure 3B

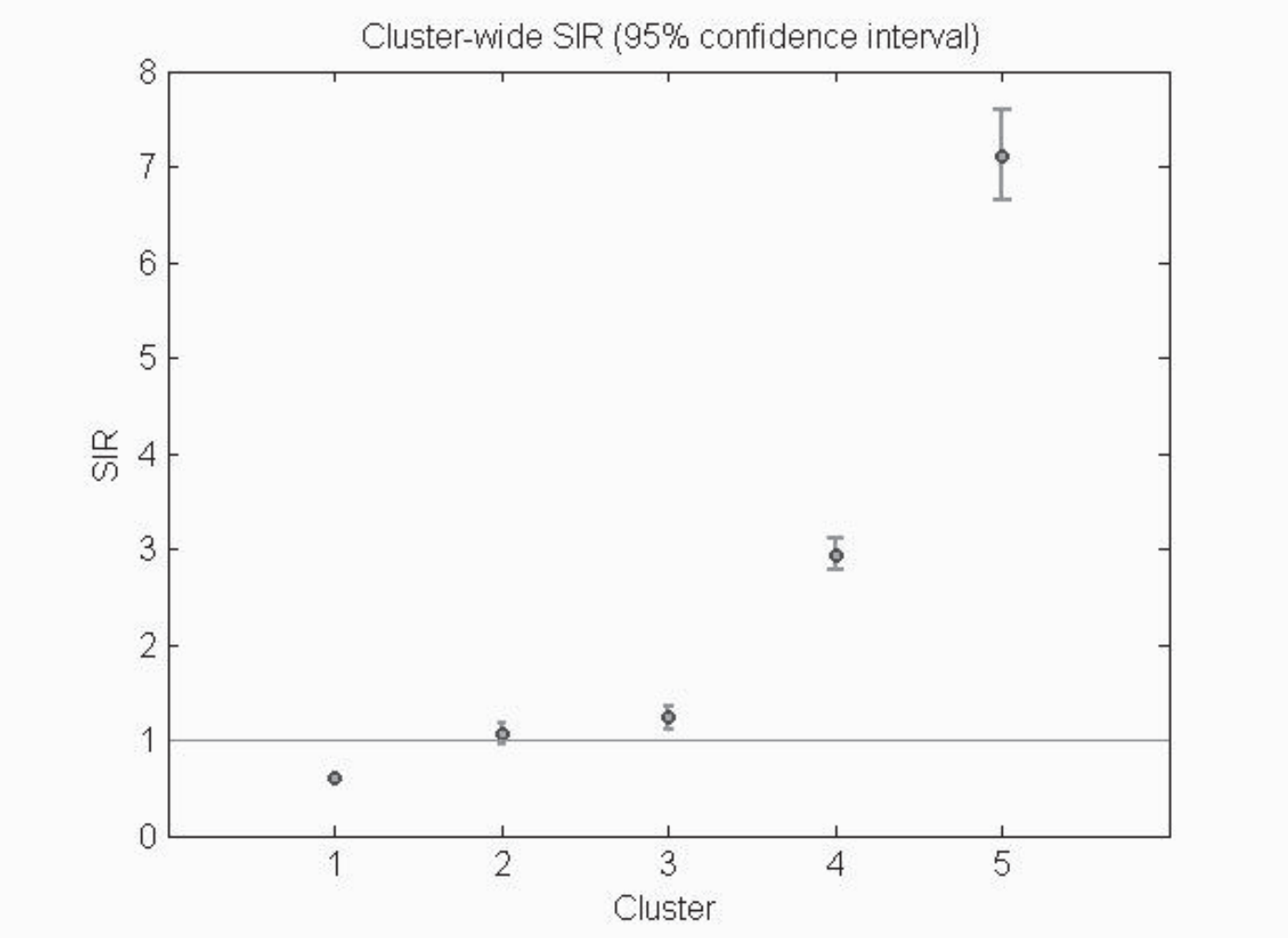

Cluster-wide SIR (95% confidence interval)
SIR
Cluster
0
1
2
3
4
5
6
7
8
1
2
3
4
5

Figure 4

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Figure 4

