

INTRODUCTION

Family history of cancer is a known risk factor for several prevalent cancer types. However, familial aggregation may not always follow the genetic linkage pattern seen with most inherited cancer syndromes and instead, may be due to unknown genetic and/or environmental risk factors. Such clustering may still confer a significant risk. This case-control study examines the association between total number of affected first and second-degree relatives and specific and general cancer risk.

STUDY AIM

The objective of this study is to examine the association between family history of cancer and cancer risk in a multi-ethnic study population.

METHODS

The Global Epidemiology Study: The Global Epidemiology Study (GES) is a multinational study to assess disease risk factors and biomarkers associated with chronic disease outcomes. Subjects were recruited to the GES from countries including the United States, Tunisia and Poland. The GES is linked to the Global Repository that houses biomaterial. Baseline blood samples were collected from all study subjects and within a three-month window of initial recruitment - medical history, demographic, and lifestyle data were obtained through a questionnaire.

Participants: We examined the association between family history of cancer and cancer risk among 9,122 cancer cases and 76,537 cancer-free controls (n=85,659). Cancer types included in this study are: brain, breast, cervical, colon, head & neck, leukemia, lung, lymphoma, ovarian, prostate, renal, skin and other gastrointestinal cancers. Controls include all the disease-free subjects as well as individuals with non-cancer chronic illnesses (arthritis, asthma, cardiovascular disease, community acquired pneumonia, diabetes, osteoporosis, rheumatoid arthritis and sepsis).

- Inclusion criteria:**
- Availability of family history of cancer data
 - Self identification of ethnicity (Tunisian Arabs were excluded due to a limited number of cases)
 - Study participants >18 years of age

Covariate Data: Data collected in the baseline questionnaire included information detailing: age, gender, ethnicity, BMI, smoking history, alcohol consumption and family history of cancer.

Statistical Analyses:

- Cross tabulations with Chi square tests and t-tests were conducted to determine the association between cancer status and potential confounders.
- Logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). The main effects model assessing the relationship between family history of cancer and cancer status, was adjusted for age, BMI and smoking pack years as continuous variables and gender & ethnicity as categorical variables.
- Potential confounding of the association between family history of cancer and cancer risk was explored using multivariate logistic regression models, including stepwise regression models. If the potential confounder caused a >20% change in the b coefficient, it was kept in the model for further analyses.
- All p-values shown are 2-sided.
- All statistical analyses were performed using STATA statistical software (STATA Corporation, College Station, TX).

RESULTS — Table 1: Crosstabs of Demographics and Health Behavior Indicators

CHARACTERISTIC	ALL CONTROLS (N=76537)	ALL CASES (N=9122)	P-VALUE	CAUCASIAN AMERICAN CONTROLS (N=33268)	CAUCASIAN AMERICAN CASES (N=5143)	P-VALUE	AFRICAN AMERICAN CONTROLS (N=5043)	AFRICAN AMERICAN CASES (N=419)	P-VALUE
Age (yr)*	58.4 [13.6]	60.3 [13.6]	<0.0001	61.1 [14.0]	64.3 [12.9]	<0.0001	54.9 [14.4]	61.7 [12.7]	<0.0001
Gender: Female Male	40302 [52.8%] 35971 [47.2%]	5244 [57.5%] 3874 [42.5%]	<0.0001	18786 [56.8%] 14300 [43.2%]	2681 [52.1%] 2460 [47.9%]	<0.0001	2801 [55.9%] 2207 [44.1%]	205 [48.9%] 214 [51.1%]	0.006
Ever used tobacco: No Yes	39011 [51.0%] 37454 [49.0%]	4739 [51.5%] 4468 [48.5%]	0.933	15101 [45.4%] 18130 [54.6%]	2098 [40.9%] 3036 [59.1%]	<0.0001	2548 [50.6%] 2486 [49.4%]	164 [39.1%] 255 [60.9%]	<0.0001
Current smoking status: No Yes	59965 [79.2%] 15776 [20.8%]	7840 [86.6%] 1214 [13.4%]	<0.0001	27338 [82.9%] 5655 [17.1%]	4436 [87.2%] 652 [12.8%]	<0.0001	3706 [74.3%] 1281 [25.7%]	342 [82.6%] 72 [17.4%]	<0.0001
Smoking pack yrs* No Yes	7.8 [18.2] 55366 [72.7%] 20780 [27.3%]	12.7 [23.8] 6479 [71.4%] 2593 [28.6%]	<0.0001	11.4 [22.9] 22291 [67.3%] 10806 [32.7%]	17.1 [27.6] 3261 [63.8%] 1852 [36.2%]	<0.0001	5.8 [12.6] 3579 [71.5%] 1428 [28.5%]	11.6 [20.5] 310 [74.3%] 107 [25.7%]	<0.0001
Alcohol: No Yes	5.5 [7.5] 28.2 [6.3]	5.5 [6.9] 25.8 [6.1]	.6938	5.7 [7.2] 29.5 [6.8]	6.2 [7.6] 27.6 [5.8]	0.0044	4.5 [5.9] 31.0 [7.6]	4.4 [5.6] 29.3 [7.0]	.78
Alcohol drinks (no.)* BMI kg/m²*	5.5 [7.5] 28.2 [6.3]	5.5 [6.9] 25.8 [6.1]	<0.0001	5.7 [7.2] 29.5 [6.8]	6.2 [7.6] 27.6 [5.8]	0.0044	4.5 [5.9] 31.0 [7.6]	4.4 [5.6] 29.3 [7.0]	.78
Family history of cancer‡: No Yes	53689 [70.1%] 22848 [29.8%]	5070 [55.6%] 4052 [44.4%]	<0.0001	17596 [52.9%] 15672 [47.1%]	1997 [38.8%] 3146 [61.2%]	<0.0001	3597 [71.3%] 1446 [28.7%]	213 [50.8%] 206 [49.2%]	<0.0001
No. relatives with cancer‡: 0 1 2 ≥3	53689 [70.2%] 14957 [19.5%] 5894 [7.7%] 1997 [2.6%]	5070 [55.5%] 2386 [26.2%] 1186 [13.0%] 480 [5.3%]	<0.0001	17596 [52.9%] 9528 [28.6%] 4489 [13.5%] 1655 [5.0%]	1997 [38.8%] 1762 [34.3%] 958 [18.6%] 426 [8.3%]	<0.0001	3597 [71.3%] 1043 [33.9%] 322 [6.4%] 81 [1.6%]	213 [50.8%] 142 [33.9%] 57 [13.6%] 7 [1.7%]	<0.0001

CHARACTERISTIC	ALL CONTROLS (N=76537)	ALL CASES (N=9122)	P-VALUE	CAUCASIAN AMERICAN CONTROLS (N=33268)	CAUCASIAN AMERICAN CASES (N=5143)	P-VALUE	AFRICAN AMERICAN CONTROLS (N=5043)	AFRICAN AMERICAN CASES (N=419)	P-VALUE
Age (yr)*	54.2 [15.1]	59.0 [15.2]	<0.0001	58.2 [12.2]	56.3 [11.8]	<0.0001	55.0 [12.0]	53.3 [12.5]	<0.0001
Gender: Female Male	2647 [59.7%] 1789 [40.3%]	123 [65.1%] 66 [34.9%]	0.137	10004 [55.5%] 8019 [44.5%]	586 [58.9%] 409 [41.1%]	0.036	6064 [38.6%] 9656 [61.4%]	1649 [69.5%] 725 [30.5%]	<0.0001
Ever used tobacco: No Yes	2932 [66.1%] 1502 [33.9%]	113 [60.1%] 75 [39.9%]	0.088	8950 [49.7%] 9074 [50.3%]	387 [38.9%] 608 [61.1%]	<0.0001	9480 [60.2%] 6262 [39.8%]	1882 [79.2%] 493 [20.8%]	<0.0001
Current smoking status: No Yes	3838 [87.3%] 556 [12.7%]	169 [90.4%] 18 [9.6%]	.221	13479 [75.1%] 4468 [24.9%]	750 [75.5%] 244 [24.5%]	.805	11604 [75.2%] 3816 [24.8%]	2143 [90.4%] 228 [9.6%]	<0.0001
Smoking pack yrs* No Yes	4.3 [12.9] 3258 [74%] 1145 [26%]	7.6 [20.8] 149 [79.3%] 39 [20.7%]	0.0011	7.2 [15.1] 12866 [71.4%] 5145 [28.6%]	15.2 [20.5] 760 [77%] 227 [23%]	<0.0001	2.3 [8.9] 13372 [85.6%] 2256 [14.4%]	2.7 [9.6] 1999 [84.5%] 368 [15.5%]	.0479
Alcohol: No Yes	4.3 [5.6] 29.3 [6.4]	7.2 [9.2] 28.9 [6.0]	0.106	4.5 [5.7] 27.6 [4.8]	3.2 [2.9] 25.9 [4.6]	0.0006	8.9 [12.6] 25.0 [4.8]	3.7 [3.2] 21.0 [4.4]	<0.0001
Alcohol drinks (no.)* BMI kg/m²*	4.3 [5.6] 29.3 [6.4]	7.2 [9.2] 28.9 [6.0]	.0031	4.5 [5.7] 27.6 [4.8]	3.2 [2.9] 25.9 [4.6]	0.0006	8.9 [12.6] 25.0 [4.8]	3.7 [3.2] 21.0 [4.4]	<0.0001
Family history of cancer‡: No Yes	3310 [74.5%] 1130 [25.5%]	98 [51.8%] 91 [48.2%]	<0.0001	14552 [80.7%] 3479 [19.3%]	595 [59.8%] 400 [40.2%]	<0.0001	14634 [92.9%] 1121 [7.1%]	2167 [91.2%] 209 [8.8%]	.003
No. relatives with cancer‡: 0 1 2 ≥3	3310 [74.6%] 849 [19.1%] 228 [5.1%] 53 [1.2%]	98 [51.9%] 57 [30.2%] 29 [15.3%] 5 [2.6%]	<0.0001	14552 [80.7%] 2672 [14.8%] 671 [3.7%] 136 [0.8%]	595 [59.8%] 280 [28.1%] 97 [9.8%] 23 [2.3%]	<0.0001	14634 [92.9%] 865 [5.5%] 184 [1.2%] 72 [0.5%]	2167 [91.2%] 145 [6.1%] 45 [1.9%] 19 [0.8%]	.001

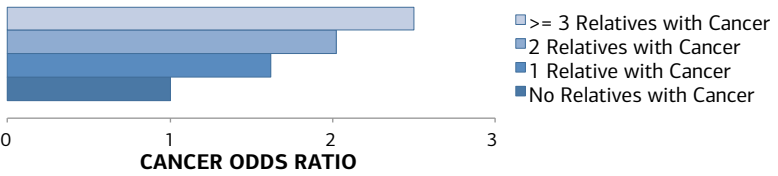
*Mean [Standard Deviation]
‡Among first degree, maternal and paternal grandparents

Table 2: Physical Activity and Diet Ovarian Cancer Risk

CHARACTERISTIC	OVERALL OR (95% CI) [CASES/ CONTROLS]	CAUCASIAN-AMERICAN OR (95% CI) [CASES/ CONTROLS]	AFRICAN-AMERICAN OR (95% CI) [CASES/ CONTROLS]
Family history of cancer‡	1.79 (1.70-1.88) [9122/76537]	1.80 (1.69-1.91) [5143/33268]	2.43 (1.97-3.00) [419/5043]
No. relatives with cancer‡: 0 1 2 ≥3	1.0 (ref) [5070/53689] 1.62 (1.53-1.72) [2386/14957] 2.02 (1.88-2.18) [1186/5894] 2.50 (2.24-2.79) [480/1997] P_trend<0.0001	1.0 (ref) [1997/17596] 1.63 (1.52-1.75) [1762/9528] 1.93 (1.77-2.10) [958/4489] 2.52 (2.24-2.85) [426/1655]P_trend<0.0001	1.0 (ref) [213/3597] 2.32 (1.84-2.93) [142/1043] 3.15 (2.28-4.37) [57/322] 1.09 (.44-2.63) [7/81]P_trend<0.0001
CHARACTERISTIC	HISPANIC/ LATINA OR (95% CI) [CASES/ CONTROLS]	CAUCASIAN-POLISH OR (95% CI) [CASES/ CONTROLS]	MIX/ OTHER OR (95% CI) [CASES/ CONTROLS]
Family history of cancer‡	2.65 (1.96-3.58) [189/4440]	2.26 (1.96-2.59) [995/18031]	1.90 (1.58-2.28) [2376/15755]
No. relatives with cancer‡: 0 1 2 ≥3	1.0 (ref) [98/3310] 2.23 (1.58-3.14) [57/849] 4.03 (2.57-6.29) [29/228] 3.17 (1.23-8.18) [5/53]P_trend<0.0001	1.0 (ref) [595/14552] 2.06 (1.77-2.40) [280/2672] 2.83 (2.24-3.58) [97/671] 3.23 (2.04-5.13) [23/136]P_trend<0.0001	1.0 (ref) [2167/14634] 1.54 (1.25-1.90) [145/865] 3.39 (2.58-5.86) [45/184] 4.42 (2.35-8.29) [19/72]P_trend<0.0001

p-value for trend estimated from logistic regression models.
*Adjusted for age, gender, BMI, ethnicity & smoking pack years
‡Among first degree, maternal and paternal grandparents

Figure 1: Number of Relatives with Cancer and General Cancer Risk for All Races



CONCLUSIONS

Family history of cancer is a known risk factor for several cancers. This case-control study shows a clear association between total number of affected first and second-degree relatives and general cancer risk. We show a dose response increase in odds ratio for cancer with increasing number of relatives with cancer. We also show that this association is true for all ethnicities studied.