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Cancer mortality in cerebral palsy in California, 1988–2002

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Abstract: *Rationale*: Exposure to lifestyle, occupational, and environmental risk factors for cancer are undoubtedly different in cerebral palsy (CP) than in the general population, and these and other differences may result in a specific pattern of cancer mortality in CP. *Objective*: To study the cancer mortality of CP in California. Study group: 40,482 CP cases (contributing 357,928 person-years) among 210,155 persons having received annual evaluations from the California Department of Developmental Services over the period 1988-2002 were followed. Methods: Mortality due to malignant and non-malignant neoplasms (ICD9 codes 140-239) in CP was compared with that in the California general population using age- and gender-standardized mortality ratios (SMRs). *Results*: An excess of mortality due to malignant neoplasms (SMR 1.31, 95% CI 1.14-1.51) was found. Cancer mortality was elevated in CP for some sites, and other cancer deaths were underrepresented in CP. Deaths due to cancer of the esophagus (SMR = 5.40, 95% CI 3.09-8.77), colon (2.16, 1.35-3.27), liver (2.21, 1.06-4.06), breast (1.83, 1.24-2.62), and bladder (4.57, 2.09-8.68) were significantly overrepresented in CP, while deaths due to cancer of the trachea, bronchus and lung were underrepresented (0.22, 0.09-0.43). Conclusion: Cancer mortality in cerebral palsy has specific differences with the population at large, and these differences may illuminate important contributing behavioral, environmental, or health care factors.

Keywords: Cancer, cerebral palsy, mortality, esophageal cancer, liver cancer, colon cancer, breast cancer, bladder cancer, lung cancer

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INTRODUCTION

Persons with cerebral palsy are known to have higher mortality rates than the age- and sex-matched general population (1-3). The magnitude of the excess varies depending on a number of risk factors, including severity of cerebral palsy (as measured primarily by level of independent motor functioning and feeding ability) and to a lesser extent presence of seizure activity and other factors. Overall mortality rates for the most severely affected children and for children and adults who are fed by gastrostomy have declined in California in recent years (4). Causes of death in cerebral palsy have been described (1,2,5), with excess deaths compared with the general population being primarily due to respiratory diseases, diseases of the digestive tract, circulatory diseases (2,5), and a number of malignant neoplasms (5). A lower than expected number of lung cancer deaths has been reported (5).

There are a number of reasons the pattern of cancer incidence and mortality may be different in cerebral palsy than in the general population. Strauss et al (5) conjectured that observed excesses in breast cancer mortality in cerebral palsy may have been due in part to substandard diagnosis and/or treatment. Other studies of developmentally disabled populations have suggested that breast cancer screening may be problematic in patients with cerebral palsy (6), and self-screening would be less frequent or effective in the CP population overall. Screening may be problematic in CP for other cancers as well. There are a number of other possible reasons for an excess number of breast cancer deaths, however, including greater frequency of nulliparity (5,7,8), and immobility (9) in cerebral palsy.

Impaired motor functioning in cerebral palsy may contribute to increased risk of cancer, as physical exercise has been shown to be protective against the development of some neoplasms, in particular hormone-related (breast, prostate) and digestive (colon) cancers (9). Persons with more severe cerebral palsy also have increased incidence of gastroesophageal reflux (10), and this has been associated with increased risk of esophageal cancer (11). Seizures are also more common among persons with cerebral palsy than in the general population (12), and seizure medications have been at

least anecdotally associated with increased risk of some cancers. Phenobarbital has been linked to the occurrence of liver tumors in some animal models (13,14). Studies in humans have not replicated this association with any antiepileptic drug (13, 14). On the other hand, certain antiepileptic drugs reportedly protect against some cancers. Phenobarbital is inversely associated with bladder cancer (15), while valproic acid apparently has some tumor suppressive effects in animal models and is now under trial for treatment of prostate cancer in humans (16).

Other possible reasons for lower rates of cancer mortality in cerebral palsy include the lower prevalence of smoking, especially among those with more severe cognitive or physical disabilities. Persons with cerebral palsy are also lighter, on average, than are those in the general population (17), and as obesity has been linked to some types of cancer (18), being lighter may protect against cancer mortality to some degree.

A study of all-cause mortality in cerebral palsy in California (4) showed that mortality rates have declined over the last few decades in children (to age 15) with very severe cerebral palsy, and in children and adults who required a feeding tube. This suggests possible improvements in the general care and treatment of persons with severe cerebral palsy that may extend to screening, diagnosis, and treatment of cancer.

Due to small population sizes in most studies of causes of mortality in cerebral palsy, and the relatively small numbers of deaths even in large cohorts, a detailed study of cancer-specific mortality rates in cerebral palsy has not been previously reported. Thus the purpose of this study is to examine carefully cancer mortality in a large cohort of persons with cerebral palsy in California. We sought to compare mortality rates overall, and in certain subgroups within this population including (a) male and female; (b) severe and not severe cerebral palsy; (c) those with and without epilepsy; and (d) early and late periods of the study.

Observed differences in patterns of cancer mortality in persons with shared attributes, such as cerebral palsy, may add significantly to the existing body of evidence connecting environmental, lifestyle, or other factors to increased or lowered risk of cancer. New hypotheses may also be generated by examining such subgroups, thus opening doors to future research.

METHODS

The population studied consists of all persons with cerebral palsy who received money or services from the State of California Department of Developmental Services (DDS) between January 1, 1988 and December 31, 2002. The DDS provides early intervention, occupational and physical therapy, equipment, case management, respite, and social services for persons with a substantial disability from cerebral palsy as defined by State regulations (19). Cerebral palsy is defined as a "(1) nonprogressive lesion or disorder in the brain occurring during intrauterine life or the perinatal period and characterized by paralysis, spasticity, or abnormal control of movement or posture which is manifest prior to two to three years of age, and (2) other significant motor dysfunction appearing prior to age 18."

Persons were identified as having cerebral palsy based on items on the Client Development Evaluation Report (CDER) (20), an instrument completed approximately annually for each person receiving services from the DDS. This report, containing over 200 medical, functional, behavioral, and cognitive items, is completed by physicians and social workers. A staff physician records data regarding medical diagnoses such as cerebral palsy and epilepsy, while others may determine the child's functional, behavioral, and cognitive status. We were interested in congenitally acquired cerebral palsy, and therefore excluded children with diagnoses suggesting cerebral palsy of postnatal origin (traumatic brain injury, near drowning, motor vehicle accident, other acquired injuries) as well as children with diagnoses suggesting an underlying disorder other than cerebral palsy (autism and degenerative disorders, and genetic or chromosomal anomalies including Down syndrome). We also excluded persons who had a diagnosis of cancer noted to be the etiology of cerebral palsy or mental retardation on their first CDER. The purpose of this exclusion was to eliminate cases where a brain tumor or other cancer and/or treatment thereof may have been the cause of an individual's diagnosis of cerebral palsy. This resulted in the exclusion of 161 persons, 84% of whom had a diagnosis of a brain tumor.

The remaining persons were the final study population. The DDS cerebral palsy data have been described in greater detail in, for example, Strauss et al (21). Reliability of pertinent CDER items has been tested and found satisfactory (22).

Mortality information was obtained from annual computer files from the State of California (1988-2002) (23) according to the ICD-9 (24). In California it is required that death certificates be filed with the state, and the electronic files are the state's official mortality records. To allow uniform comparisons across all years,

ICD-10 codes for causes of death reported in 1999-2002 were recoded into ICD-9 codes when necessary.

Cancer-specific mortality rates in the cerebral palsy cohort were compared with those in the California general population as follows:

- For each cause of death considered, age-specific mortality rates (deaths per 100,000 person-years of exposure) in the California general population were computed using state mortality (23) and population (25) data over the time period 1988-2002. Sex was also adjusted for in some analyses.
- For subjects with cerebral palsy the total number of person-years lived by the cohort in each age group was determined.
- Mortality rates from step 1 were multiplied by the person-years at risk from step 2 to determine expected numbers of deaths due to each cause within each age group. The expected numbers in each age group were summed to give the total expected number of deaths for each cause.
- The observed number of deaths in the cerebral palsy cohort associated with each cause of death was noted.
- Standardized mortality ratios (SMRs) for each cause of death were computed as the ratio of the observed number of deaths to the expected number (26).
- Confidence intervals for the SMRs were constructed based on the assumption that the observed number of deaths follows a Poisson distribution (26).

Similar comparisons were made for various subgroups of cerebral palsy and/or the general population. These included (a) males and females; (b) severe and not severe cerebral palsy; (c) those with and without epilepsy; and (d) early (1988-1995) and late (1996-2002) periods.

RESULTS

After exclusions as described and justified above, a total of 40,482 persons (22,362 male, 55%) with cerebral palsy age 2 years and older during the study period January 1, 1988 to December 31, 2002 were identified. The mean age was 16.9 years (SD = 15.5) at first (CDER) evaluation and they contributed 357,928 person-years of exposure during the study period. Of the 4,092 persons who died during the study period, 221 had underlying cause of death indicated to be a malignant or non-malignant neoplasm (ICD9 codes 140-239). Table 1 shows the breakdown of person-years of follow-up according to the subgroups considered in the study.

Table 1. *Person-years of exposure for various subgroups within the cerebral palsy (CP) population.*

Group	Person-years (%)
All (ages 2 and older)	357,828 (100)
Gender	
Male	195,033 (54)
Female	162,894 (46)
Severity of CP	
Severe	80,872 (23)
Not severe	277,055 (77)
Epilepsy (any history of)	
Yes	157,044 (44)
No	200,883, (56)
Period	
Early (1988-1995)	169,791 (47)
Late (1996-2002)	188,136 (53)

Table 2 shows the observed and expected numbers of deaths with SMRs and 95% confidence intervals for all cancers and various specific cancer sites. Overall an excess in tumor-related mortality was seen in the cerebral palsy cohort, with SMR = 1.43 (95% CI 1.25-1.63). The pattern was quite heterogeneous across sites, however.

Three deaths due to neoplasms of lip, oral cavity, and pharynx were expected, whereas two were observed, a non-significant difference (SMR = 0.67, 0.08-2.43). An excess of deaths due to cancers of digestive organs and peritoneum was observed in the cerebral palsy cohort (SMR = 2.01, 1.56-2.56). Specific organs in this category showing a significant excess of deaths were the esophagus (SMR = 5.40, 3.09-8.77), colon (SMR = 2.16, 1.35-3.27), and liver (SMR = 2.21, 1.06-4.06). The differences from general population mortality rates for this group of cancers were consistent across the sub-groups considered with the exceptions of colon cancer in males (SMR = 2.54, 1.39-4.25) versus females (SMR = 1.71, 0.74-3.36), and esophageal cancer in severe cerebral palsy (SMR = 9.51, 3.82-19.59) versus in the not severe group (SMR = 4.04, 1.85-7.67).

Deaths due to respiratory and intrathoracic organ tumors were underrepresented in cerebral palsy (SMR = 0.26, 0.13 - 0.48). Most of this protective effect was due to a lack of lung cancer deaths, where 8 deaths were observed, while 36.5 were expected (SMR = 0.22, 0.09-0.43). For all other causes within this category, no significant difference was observed (SMR = 1.36, 0.16-4.92). The SMR for this category of cancer deaths was consistent across all subgroups considered, including the early and late periods of the study.

Table 2. *Observed numbers of deaths in the cerebral palsy (CP) population, and expected numbers of deaths based on California general population mortality rates for malignant and non-malignant neoplasms.*

Cause of death	ICD9 Codes	Deaths		SMR‡	95% C.I.§
		Obs*	Exp†		
All neoplasms	140-239	221	154.8	**1.43**	1.25 - 1.63
All malignant neoplasms	140-208	201	152.94	**1.31**	1.14 - 1.51
Lip, oral cavity, and pharynx	140-149	2	2.97	**0.67**	0.08 - 2.43
Digestive organs and peritoneum	150-159	67	33.29	**2.01**	1.56 - 2.56
Esophagus	150	16	2.96	**5.40**	3.09 - 8.77
Not severe	150	9	2.23	**4.04**	1.85 - 7.67
Severe	150	7	0.74	**9.51**	3.82 - 19.59
Colon	153	22	10.19	**2.16**	1.35 - 3.27
Colon female	153	8	4.69	**1.71**	0.74 - 3.36
Colon male	153	14	5.52	**2.54**	1.39 - 4.25
Liver	155	10	4.53	**2.21**	1.06 - 4.06
Other digestive organs		153	135	**1.13**	0.96 - 1.33
Respiratory, intrathoracic organs	160-165	10	37.99	**0.26**	0.13 - 0.48
Trachea, bronchus, lung	162	8	36.52	**0.22**	0.09 - 0.43
Other		2	1.47	**1.36**	0.16 - 4.92
Bone, connective tissue, skin, breast	170-176	40	23.43	**1.71**	1.22 - 2.33
Breast (female only)	174	30	15.56	**1.93**	1.30 - 2.75
Other		10	7.07	**1.41**	0.68 - 2.60
Genitourinary organs	179-189	23	19.21	**1.20**	0.76 - 1.80
Bladder	188	9	1.97	**4.57**	2.09 - 8.68
Male	188	3	1.38	**2.18**	0.45 - 6.36
Female	188	6	0.57	**10.46**	3.84 - 22.77
Male genitourinary	185-187	4	5.11	**0.78**	0.21 - 2.01
Female genitourinary	179-184	6	8.82	**0.68**	0.25 - 1.48
Other genitourinary		4	3.31	**1.21**	0.33 - 3.10
Other and unspecified sites	190-199	29	17.40	**1.67**	1.12 - 2.39
Brain	191	17	6.70	**2.54**	1.48 - 4.06
Other		12	10.70	**1.12**	0.58 - 1.96
Lymphatic and hematopoietic tissue	200-208	30	18.64	**1.61**	1.09 - 2.30
Lymphomas	200-202	14	7.71	**1.82**	0.99 - 3.05
Leukemias	204-208	15	8.43	**1.78**	1.00 - 2.94
Multiple myeloma and immunoproliferative neoplasms	203	1	2.51	**0.40**	0.01 - 2.22
Tobacco-related cancers‖	See footnote	72	71.13	**1.01**	0.79 - 1.27
Alcohol-related cancers¶	See footnote	80	27	**2.96**	2.35 - 3.96
Benign neoplasms, carcinoma in situ, neoplasms of uncertain behavior or unspecified nature	210-239	20	1.66	**12.06**	7.37 - 18.63
Benign neoplasms	210-229	5	0.47	**10.74**	3.49 - 25.07
Carcinoma in situ	230-234	0	0.00	**0.00**	0.00 - 1733.55
Neoplasms of uncertain behavior	235-238	8	0.34	**23.80**	10.27 - 46.89
Neoplasms of unspecified nature	239	7	0.85	**8.19**	3.29 - 16.88

* Obs = number of observed deaths among 14,781 persons with cerebral palsy in California, 1988-2002; † Exp = expected numbers of deaths based on age- and sex-adjusted cause-specific mortality rates in California general population, 1988-2002; ‡ Ratio of observed to expected number of deaths; § Confidence interval based on the assumption that the observed deaths follow a Poisson distribution; || Tobacco related cancers from Monograph 83 of the IARC on tobacco smoking (27): lung, trachea, bronchus (ICD9 codes 162), oral cavity (140-145), pharynx (oro-, naso-, hypo-) (146-148), larynx (161), esophagus (150), pancreas (157), bladder and renal pelvis (188), nasal cavities and sinuses (160), stomach (151), liver (155), kidney (189), uterine cervix (180), myeloid leukemia (205); ¶Alcohol-related cancers as reported by the World Cancer Research Fund and the American Institute for Cancer Research (28): Mouth and pharynx (140-149), larynx (161), esophagus (150), colon and rectum (153-154), liver (155), and breast (174-175).

Deaths due to bone, connective tissue, skin, and breast (ICD9 170-176) were more numerous than expected in cerebral palsy (SMR = 1.71, 1.22-2.33). For males, there was no significant excess (SMR = 1.32, 0.48-2.86 - not shown in Table 2), and most of the excess in women was due to breast cancer (ICD9 174), with 30 observed deaths and 16 expected (SMR = 1.93, 1.30-2.75). There was a suggestion (not shown in table 2) of a smaller excess number of breast cancer deaths for 1996-2002 (SMR = 1.51, 0.83-2.54) compared with the early period 1988-1995 (SMR = 2.54, 1.45-4.13).

Neoplasms of genitourinary organs overall showed no significant excess (SMR = 1.20, 0.76-1.80); however bladder cancer was overrepresented in cerebral palsy (SMR = 4.57, 2.09-8.68), more so in females (SMR = 10.46, 3.84-22.77) than in males (SMR = 2.18, 0.45-6.36). Deaths due to male genitourinary tumors overall were slightly underrepresented with 4 deaths observed while 5 were expected, but this did not reach statistical significance (SMR = 0.78, 0.21-2.01). The same was true for all female genitourinary cancers with 6 observed and 9 expected (SMR = 0.68, 0.25-1.48).

Among malignant neoplasms in other and unspecified sites (ICD9 codes 190-199) only deaths due to brain cancer were overrepresented in cerebral palsy, with 17 observed deaths and fewer than 7 expected (SMR = 2.54, 1.48-4.06). Only 12 deaths were observed for other cancers in this category, with approximately 11 expected.

Lymphatic and hematopoietic tissue neoplasms were responsible for 30 deaths, while slightly fewer than 19 were expected (SMR = 1.61, 1.09-2.30). Lymphomas (SMR = 1.82, 0.99-3.05) and leukemias (SMR = 1.78, 1.00-2.94) contributed approximately equally to the overall excess in this category.

The above categories exhaust the malignant neoplasms (ICD9 codes 140-208). The remaining neoplasms (ICD9 codes 210-239) were benign neoplasms (ICD9 codes 210-229), carcinoma in situ (ICD9 codes 230-234), and neoplasms of uncertain behavior (ICD9 codes 235-238) or unspecified nature (ICD9 codes 239). In these categories overall, fewer than 2 deaths were expected while 20 were observed (SMR = 12.06, 7.37-18.63). None of the excess was attributable to carcinoma in situ, where no deaths were observed and essentially none was expected. Benign neoplasms (SMR = 10.74, 3.49-25.07), neoplasms of uncertain behavior (23.80, 10.27-46.89), and neoplasms of unspecified nature (8.19, 3.29-16.88) all contributed to the overall excess here. The excess in each of these categories declined from the early to late periods (not shown in table 2).

Tobacco use, especially smoking, has been implicated in the development of a number of malignant neoplasms (27) (See footnote to table 2 for the complete list). Deaths due to these cancers as a whole occurred with equal frequency in cerebral palsy and California in general with SMR = 1.01 (0.79-1.27). However, as indicated above, deaths due to cancer of the trachea, bronchus, and lung (the group of cancers most closely related to tobacco) were clearly underrepresented in cerebral palsy. This protective effect was uniform across most subgroups (males and females, severe and not severe, early and late), but was more pronounced (not shown in table 2) in persons without epilepsy (SMR = 0.09, 0.01-0.31) than in those with epilepsy (0.45, 0.16-0.97). The observed protective effect against lung cancer was counterbalanced by observed excesses of mortality due to other partly tobacco-related cancers (which have additional risk factors other than tobacco) including esophagus, liver, and bladder and renal pelvis.

Alcohol has also been implicated in the development of some tumors (28) (see footnote to table 2 for the complete list) and mortality due to these neoplasms was three times as common in cerebral palsy as in the general population (SMR = 2.96, 2.35-3.96). The excess mortality among these cancers was concentrated in esophageal, liver, colon, and breast. The SMRs for alcohol-related cancers were consistent across most subgroups; however as mentioned above, esophageal cancer mortality was more common in those with severe cerebral palsy (SMR = 9.51, 3.82-19.59) than in others, and mortality in breast cancer was somewhat higher in the early period of the study than the late.

DISCUSSION

Although it is clear that persons with cerebral palsy experience more cancer deaths than expected overall, the pattern of excess risk is not homogeneous across cancer sites. Lung cancer deaths are substantially underrepresented, whereas excesses are seen in deaths from esophageal, liver, bladder, colon, and breast cancers. There are a number of possible reasons for the heterogeneity of the excesses of deaths by type of cancer in this population. These reasons include differences in exposure to known carcinogens (e.g., tobacco, alcohol, or workplace exposures), and of course premature death in cerebral palsy due to other causes, thus precluding development of some cancers that may be associated with old age. Yet, as this study presents age-adjusted comparisons of mortality rates, the young age at death is not an explanation for the deficits observed for some cancer sites.

That there is not an overall protective effect in

cerebral palsy for tobacco-related cancers may be somewhat surprising, as the prevalence of smoking in this population must be lower than in the general population. The anticipated protective effect of not smoking is very clear for cancer of the trachea, bronchus, and lung. Excess numbers of deaths due to other cancers linked to tobacco counter balance this protective effect. These other cancers are associated with a number of risk factors other than tobacco, some of which are known to be more common in persons with cerebral palsy. For example, gastroesophageal reflux disease (GERD) is a risk factor for esophageal cancer, and GERD is also known to be more common in persons with cerebral palsy. Feeding problems resulting in the need for a gastrostomy tube for feeding are more common in the group with severe cerebral palsy, and this subgroup is at especially high risk of GERD. Thus the higher SMR we report for esophageal cancer mortality in severe cerebral palsy is not surprising. Liver cancer is increased in persons with a history of hepatitis B and C (29), and these viral infections have been noted to occur more frequently in populations of intellectually disabled persons (30). Similarly, an increased incidence of bladder infections in cerebral palsy may contribute to the excess mortality for bladder tumors.

An excess risk of cancers linked to alcohol consumption (28) was also observed in our cerebral palsy cohort, and again this is likely due to risk factors common in cerebral palsy other than alcohol. In this context, esophageal and liver cancers have been discussed above. The excess colon cancer mortality may in part be associated with the limited mobility of most subjects in the cerebral palsy population. Exercise has been shown to protect against colon cancer, with physically active men and women experiencing about half the risk of those who are not active (9). In the present study, however, we did not find a higher SMR for the severe cerebral palsy group, who are more sedentary than the mild (not severe) group. Dietary differences in the cerebral palsy population may also contribute to excess risk of colon cancer, though we are unaware of any research that would confirm this and lack information on diet in our population.

The excess breast cancer mortality may be associated with substandard diagnosis or treatment, as has been suggested (5). The present study may lend some support to this hypothesis, as we see a decrease in the SMR for breast cancer from early to late periods (though the difference is not statistically significant). This may be related to improvements in attitudes in the health care profession in California, and in changes in laws and policy regarding care and treatment of persons with cerebral palsy and other developmental disabilities. It seems unlikely, on the other hand, that frequency of self-breast-examination, which is a major method of detection of breast cancer in the general population, might have increased more significantly in the CP cohort than in the general population. The lower than average incidence of pregnancy in the cerebral palsy cohort may also play a role here, as it has been suggested is the case with Catholic nuns and others who are unlikely to bear children (7, 31). Finally, higher levels of physical activity have also been found to protect against breast cancer, with occupational, leisure, and household activities being associated with a 30% reduction in breast cancer rates (9).

The excess we report for deaths due to brain tumors (SMR=2.54, 1.48-4.06) is not as large as described previously in a study based on similar sources of data (SMR = 9.50, 6.72-13.04 - derived from table III of the cited study) (5). In this study, unlike in the previous study, we excluded persons with an initial diagnosis of any malignant neoplasm as an etiology for CP, and most (85%) of those exclusions were for brain tumors. Why there remains an overrepresentation of brain tumor deaths in persons with cerebral palsy after such exclusions is not clear.

Our study is subject to a number of limitations. First, persons with very mild CP may have been preferentially lost to follow-up if they felt they did not need continued services from the DDS. If this were the case, it would result in a study population that includes a greater proportion of more severe cerebral palsy, and thus the results may not apply to the mildest cases or the most general population of CP. Second, because the cerebral palsy cohort was quite young, very small numbers of deaths were observed for many cancer sites. Thus we had limited power to detect small differences in mortality rates for many specific sites. Also, we did not have information on cancer incidence in our CP population. Thus we cannot know to what extent our findings may reflect differences in incidence of cancer in CP as opposed to differences in cancer screening or treatment.

These limitations are offset by several strengths. The size of the CP cohort and the detailed information on underlying causes of death enabled us to detect differences in mortality rates for a number of specific cancer sites, and to make comparisons in a number of subgroups. The use of the identical source of mortality information for the reference group (California general

population) and the CP cohort is another strength of the study, as it minimizes the effect on the resulting SMRs of a number of potential sources of reporting bias.

The information provided here adds to the body of evidence suggesting an association with cancer of a number of risk factors, including gastroesophageal reflux for esophageal cancer, hepatitis for liver cancer, smoking for lung cancer, and sedentary lifestyles for colon and breast cancer. The results may raise awareness of potential areas for improvement in cancer screening and treatment in developmentally disabled populations. A number of questions arise here that we hope may encourage further research.

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