

Low risk of solid tumors in persons with Down syndrome

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Purpose: The aim of this study was to investigate cancer incidence in a large cohort of persons with Down syndrome.

Methods: Down syndrome was identified from the Danish Cytogenetic Register. Cancer occurrence was identified by linkage to the Danish Cancer Registry. Standardized incidence ratios (SIRs) and 95% confidence intervals (CIs) were calculated based on observed and expected numbers from rates for all Danish residents. The cohort consisted of 3,530 persons with Down syndrome contributing 89,570 person-years at risk.

Results: Acute leukemia risk was highest from 1–4 years of age and remained elevated until age 30. The overall risk of solid tumors was decreased (SIR 0.45; 95% CI 0.34–0.59), especially in persons

50 years or older (SIR 0.27; 95% CI 0.16–0.43). We found a significantly lower risk of lung cancer (SIR 0.10; 95% CI 0.00–0.56), breast cancer (SIR 0.16; 95% CI 0.03–0.47), and cervical cancer (SIR 0.0; 95% CI 0.00–0.77). Testicular cancer was the only solid tumor with an increased SIR (2.9; 95% CI 1.6–4.8).

Conclusions: The risk of all major groups of solid tumors was decreased, except testicular cancer. Altered screening strategies should be considered for persons with Down syndrome. This unusual pattern of cancer occurrence may help understanding carcinogenesis in the general population.

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Key Words: cancer; Down syndrome; tumor-suppressor genes

INTRODUCTION

Down syndrome is the most common chromosome abnormality in humans, occurring in about 1 in 800 live births.¹ Down syndrome is associated with a number of characteristic dysmorphic features and congenital or acquired medical problems.² The pattern of cancer during childhood is unique: leukemias constitute more than 95% of cancers among children with Down syndrome, compared with about 35% of cancers among children in the general population.³ The survival of individuals with Down syndrome has increased in recent decades (owing mainly to improved management of congenital heart defects), resulting in large numbers of adults with Down syndrome.⁴ There is a need for studies of health issues in this growing population. Previous studies have suggested a lower incidence of solid tumors in adults with Down syndrome, but the results have been limited by the inclusion of a relatively small proportion of older individuals.^{5–8} We compared the frequency of cancer in a large, unselected cohort of persons with cytogenetically diagnosed Down syndrome, including almost 7,000 person-years of observation over 50 years of age, with the frequency in the Danish general population.

MATERIAL AND METHODS

Study protocol

This was a registry-based follow-up study of persons with Down syndrome in Denmark. The cohort was identified from

the Danish Cytogenetic Register and linked to the Danish Cancer Registry. Data linkage was based on the personal identification number assigned to each resident either in April 1968 or thereafter at the time of birth or arrival in Denmark. The personal identification number is unique to each resident and allows complete follow-up in the national civil status (including death, emigration, and immigration) and health-related registries. This study was approved by the Danish Data Protection Agency.

Study cohort

The Danish Cytogenetic Register was founded in 1968 with the aim of collecting information on chromosomal abnormalities in Denmark. The register is based on reports from all cytogenetic laboratories throughout the country and is believed to provide virtually complete ascertainment of constitutional chromosomal abnormalities diagnosed in Denmark since 1961.⁹ By December 2007, the Cytogenetic Register contained information on 3,551 persons with a postnatal cytogenetic diagnosis of Down syndrome and a verified personal identification number and residence in Denmark at the time of the cytogenetic study. A karyotype derived from peripheral blood was available from all persons. Cytogenetic diagnoses from the 1960s and 1970s reported as trisomy G were accepted as trisomy 21. People studied with only fluorescence in situ hybridization analysis were

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not included. All reported karyotypes were reviewed by three authors (S.A.R., J.M.F., and H.H.), and additional data from the reporting cytogenetic laboratory were requested when necessary. After review, five persons were reclassified as not having trisomy 21 and were excluded from the study. People with cytogenetic abnormalities in addition to trisomy 21 were also excluded: XYY ($n = 1$), XXY ($n = 2$), XXX ($n = 3$), translocations ($n = 7$), inversions ($n = 2$), and deletion ($n = 1$).

Cancer follow-up

Cancer occurrence was identified by linkage to the Danish Cancer Registry, which has received notifications of malignant diseases from all clinical and pathological departments in the country since 1943. Notifications to the registry are supplemented by examination of all death certificates for cancer diagnoses. The registry provides practically complete coverage of the occurrence of cancer in Denmark.¹⁰

Only cancers occurring after the introduction of the personal identification number on 1 April 1968 were selected from the Danish Cancer Registry. Person-years at risk were counted from 1 April 1968, or the date of birth for those born later, until date of death, emigration, or 31 December 2012, whichever occurred first. All cancers were classified according to the International Classification of Diseases, 10th Revision.

Statistical analysis

The cohort members were followed from birth (or 1 April 1968 for persons born before that date) until time of death, emigration, or the end of follow-up (31 December 2012), whichever came first. Information on emigration was obtained from the Civil Registration System.

The numbers of cancer cases in the study cohort were compared with the expected numbers calculated from rates for all Danish inhabitants specific for sex, 5-year age group, and calendar period. The standardized incidence ratio (SIR) was calculated as the ratio of the observed to the expected incidence. Statistical evaluation was based on the calculation of 95% confidence intervals (CIs) on the assumption that the observed numbers of cases followed a Poisson distribution. If the CI excluded 1, the SIR was considered to be significantly different from expected.

Lifetime cumulative rates of solid tumors and leukemias were calculated in 5-year age groups for the Down syndrome cohort and the general population.

RESULTS

The final cohort consisted of 3,530 persons with Down syndrome (1,928 males and 1,602 females) born between 1878 and 2007. Based on karyotype, they were classified as standard trisomy 21 ($n = 3,272$; 92.7%), Robertsonian translocations ($n = 144$; 4.1%), or mosaicism (mixture of cells with normal karyotype and trisomy 21) ($n = 114$; 3.2%). The cohort contributed 89,570 person-years at risk with 48,136 years of risk among

Table 1. Cytogenetic groups, year of birth, and person-years at risk by sex

	Male ($n = 1,928$; 55%)	Female ($n = 1,602$; 45%)	Total ($n = 3,530$)
Cytogenetic groups			
Standard trisomy 21	1,803 (93.5%)	1,469 (91.7%)	3,272 (92.7%)
Mosaicism	48 (2.4%)	66 (4.1%)	114 (3.2%)
Robertsonian translocations	77 (4.0%)	67 (4.2%)	144 (4.1%)
Year of birth			
Before 1920	14	29	43
1920–1939	106	124	230
1940–1959	316	242	558
1960–1979	663	548	1,211
1980–1999	645	491	1,136
2000–2007	184	168	352
Person-years at risk, by age			
Total	48,747	40,823	89,570
0–4	—	—	10,410
5–9	—	—	10,857
10–14	—	—	10,478
15–19	—	—	9,690
20–24	—	—	8,913
25–29	—	—	8,117
30–34	—	—	7,426
35–39	—	—	6,594
40–44	—	—	5,608
45–49	—	—	4,521
50–54	—	—	3,270
55–59	—	—	2,098
≥60	—	—	1,589

persons 20 years of age or older and 6,957 years at risk among persons 50 years of age or older (Table 1).

The overall risk of cancer was not significantly different from what was expected (SIR 0.84; 95% CI 0.70–1.02) (Table 2). Lymphomas and leukemias were more frequent than expected among persons with Down syndrome (SIR 5.5; 95% CI 4.2–7.1), and solid tumors were less frequent than expected (SIR 0.45; 95% CI 0.34–0.59). The risk of all major groups of malignant solid tumors was decreased, with the exception of testicular cancer (SIR 2.9; 95% CI 1.6–4.8). Most notable were the very low risk of lung cancer (SIR 0.10; 95% CI 0.00–0.56), skin cancer (SIR 0.24; 95% CI 0.10–0.48), cervical cancer (SIR 0.0; 95% CI 0.00–0.77), and female breast cancer (SIR 0.16; 95% CI 0.03–0.47). Only 3 cases of breast cancer (carcinomas at age 31, 47, and 55 years) were observed versus 18.6 cases expected.

Testicular cancer was diagnosed in 14 males with Down syndrome (median age 35 years, range 18–45 years). Histology of the testicular tumors showed seminoma ($n = 9$), teratocarcinoma ($n = 1$), embryonal carcinoma ($n = 3$), and mixed

Table 2. Standardized incidence ratios and observed and expected numbers by cancer site among 3,530 persons with Down syndrome

Site (ICD-10 codes)	Observed (n)	Expected (n)	SIR	95% CI
All sites (C00–C14)	113	134	0.84	0.70–1.02
Buccal cavity (C00–C14)	0	3.20	0.0	0.00–1.15
Digestive system (C15–C26)	8	15.3	0.52	0.22–1.03
Esophagus (C15)	1	0.99	1.01	0.01–5.60
Stomach (C16)	3	1.81	1.65	0.33–4.83
Colon (C18–C19)	2	5.37	0.37	0.04–1.34
Rectum (C20–C21)	0	3.27	0.0	0.00–1.13
Liver (C22)	1	0.84	1.19	0.02–6.65
Gall bladder (C23–C24)	0	0.44	0.0	0.00–8.38
Pancreas (C25)	0	1.92	0.0	0.00–1.92
Respiratory system (C30–C39)	1	11.5	0.09*	0.00–0.49
Lung (C33–C34, C39)	1	10.0	0.10*	0.00–0.56
Bone and cartilage (C40–C41)	0	0.72	0.0	0.00–5.12
Skin (C43–C44)	8	32.9	0.24*	0.10–0.48
Melanoma (C43)	2	8.10	0.25*	0.03–0.89
Nonmelanoma (C44)	6	24.8	0.24*	0.09–0.53
Mesothelioma and soft tissue (C45–C49)	3	1.59	1.58	0.32–4.60
Breast (C50)	3	18.6	0.16*	0.03–0.47
Female genital organs (C51–C58)	5	10.6	0.47	0.15–1.10
Cervix (C53)	0	4.79	0.0*	0.00–0.77
Uterus (C54–C55, C58)	2	2.49	0.80	0.09–2.90
Ovary (C56–C574)	3	2.87	1.04	0.21–3.05
Male genital organs (C60–C63)	14	8.64	1.62	0.89–2.72
Prostate (C61)	0	3.57	0.0	0.00–1.03
Testis (C62)	14	4.88	2.87*	1.57–4.82
Urinary tract (C64–C68)	5	6.77	0.74	0.24–1.72
Kidney (C64)	0	2.29	0.0	0.00–1.61
Pelvis and ureter (C65–C66)	1	0.42	2.36	0.03–13.1
Bladder (C67)	4	3.99	1.00	0.27–2.57
Eye, brain, CNS (C69–C72)	5	9.06	0.55	0.18–1.29
Eye (C69)	1	0.54	1.85	0.02–10.3
Brain (C71, C751–C753)	3	5.86	0.51	0.10–1.49
Medulla, cranial nerves, and unspecified (C72)	1	1.23	0.81	0.01–4.52
Endocrine organs (C73–C74)	0	1.54	0.0	0.00–2.40
Other and poorly specified sites (C76–C80)	3	2.43	1.24	0.25–3.61
All solid tumors (C00–C80)	55	121	0.45*	0.34–0.59
All lymphomas and leukemia (C81–C96)	58	10.6	5.50*	4.17–7.11
Hodgkin lymphoma (C81)	1	1.86	0.54	0.01–3.00
Non-Hodgkin lymphoma (C82–C85, C883–C889)	2	3.62	0.55	0.06–2.00
Myeloma (C90, C880–C882)	0	0.86	0.0	0.00–4.29
Leukemia (C91–C96)				
Lymphoid leukemia (C91)	30	2.31	13.0*	8.74–18.5
Myeloid leukemia (C92)	19	1.61	11.8*	7.11–18.5
Monocytoid leukemia (C93)	1	0.05	21.9	0.20–122
Other leukemias (C94–C95)	5	0.22	23.2*	7.48–54.2

CI, confidence interval; CNS, central nervous system; ICD, International Classification of Diseases, 10th revision.

*Standardized incidence ratios (SIRs) significantly different from 1.

Table 3. Standardized incidence ratios and observed and expected numbers of all malignancies^a according to sex and type of constitutional cytogenetic abnormalities

	Observed (n)	Expected (n)	SIR	95% CI
Sex				
All malignancies				
Males	61	60.9	1.00	0.77–1.29
Females	52	72.8	0.71	0.53–0.94
Solid tumors (ICD-10 codes C00–C80)				
Males	33	53.5	0.62	0.42–0.87
Females	22	67.4	0.33	0.20–0.49
Lymphomas and leukemias (ICD-10 codes C81–C96)				
Males	28	6.47	4.33	2.88–6.26
Females	30	4.09	7.34	4.95–10.5
Constitutional karyotype				
All malignancies				
Standard trisomy 21	104	122	0.85	0.70–1.03
Robertsonian translocations	2	4.83	0.41	0.05–1.50
Mosaicism	7	6.89	1.02	0.41–2.09
Solid tumors (ICD-10 codes C00–C80)				
Standard trisomy 21	50	110	0.45	0.34–0.60
Robertsonian translocations	1	4.32	0.23	0.00–1.29
Mosaicism	4	6.34	0.63	0.17–1.62
Lymphomas and leukemias (ICD-10 codes C81–C96)				
Standard trisomy 21	54	9.68	5.58	4.19–7.28
Robertsonian translocations	1	0.40	2.47	0.03–13.8
Mosaicism	3	0.47	6.45	1.30–18.8

CI, confidence interval; ICD, International Classification of Diseases, 10th Revision; SIR, standardized incidence ratio.

^aMalignancies were analyzed combined and analyzed separately for solid tumors and leukemias.

germ-cell tumor ($n = 1$). The nine seminomas were diagnosed in a narrow age range of 33–41 years.

Females had a lower risk for solid tumors and a higher risk of leukemia than males (Table 3). The sex difference for solid tumor risk was attributable entirely to testicular cancer in males.

The SIR of solid tumors significantly decreased after 40 years of age (Table 4) and was lowest among persons 50 years or older (SIR 0.27; 95% CI 0.16–0.43). Cancer was diagnosed in 46 children younger than 15 years of age, including 44 with acute leukemias (96%), one infant with unilateral retinoblastoma, and one 9-year-old boy with Hodgkin lymphoma. The number of solid tumors among persons between 15 and 30 years of age was close to the expected number (SIR 1.23; 95% CI 0.59–2.26). The malignancies in this age group were dominated by germ-cell tumors (6 of 10 solid tumors).

The risk of leukemia was very high in children younger than 5 years of age, with an SIR of 27 for acute lymphoblastic leukemia (ALL) and 114 for acute myeloid leukemia (Table 5). The elevated risk of leukemia persisted until 30 years of age but with a higher risk for ALL than for acute myeloid leukemia. Three cases of acute leukemia were diagnosed after 30 years of age (versus the 2.0 cases expected).

The lifetime cumulative rates of leukemia at 5, 10, 30, and 60 years of age among those with Down syndrome and the general population were 1.9, 2.0, 2.5, and 2.9% vs. 0.04, 0.06, 0.11,

and 0.32%, respectively. The corresponding cumulative rates of solid tumors at 30 and 60 years of age were 0.6 and 5.0% for those with Down syndrome versus 0.6 and 11.3% for the general population.

DISCUSSION

This cohort study of more than 3,500 persons with cytogenetically confirmed Down syndrome provides more precise estimates of the Down syndrome–associated cancer risk than previous studies, especially for adults. This includes better estimates of the increased risk of leukemia among children and young adults, and of testicular cancer among young adults, but also of the markedly decreased risk of several solid tumors.

Compared with a previous study of a subgroup of the same cohort,⁵ the person-years at risk increased from 48,453 to 89,571, the person-years at risk from those above 40 years of age increased from 6,991 to 17,086, and the number of expected cancers increased from 50 to 134.

The risk and types of cancers that occur in people with Down syndrome are strongly influenced by age. This is also true in the general population, but the pattern of cancer sites is very different in people with Down syndrome. At younger ages the overall risk is high because of the much higher risk of leukemias, but in the adult population, the risk is much lower because of the significantly decreased occurrence of solid tumors in older

Table 4. Standardized incidence ratios and observed and expected numbers of solid tumors in 5-year age groups

Age group (years)	Observed (n)	Expected (n)	SIR	95% CI
0–4	1	1.2	0.85	0.01–4.73
5–9	0	0.7	0.00	0.00–5.33
10–14	0	0.7	0.00	0.00–5.41
15–19	4	1.3	3.08	0.83–7.89
20–24	1	2.5	0.40	0.01–2.22
25–29	5	4.4	1.15	0.37–2.68
30–34	5	6.7	0.74	0.24–1.74
35–39	7	9.6	0.73	0.29–1.50
40–44	6	13.6	0.44	0.16–0.96
45–49	9	17.7	0.51	0.23–1.96
50–54	6	19.7	0.31	0.11–0.66
55–59	5	18.8	0.27	0.09–0.62
≥60	6	24.2	0.25	0.09–0.54
Total	55	120.9	0.45	0.34–0.59

CI, confidence interval; SIR, standardized incidence ratio.

Table 5. Standardized incidence ratios and observed and expected numbers of acute lymphoblastic and myeloid leukemia according to age

Age group	Observed ^a (n)	Expected (n)	SIR	95% CI
Acute lymphoblastic leukemia (ICD-10 code C91)				
0	0	0.07	0	—
1	1	0.12	8.2	0.1–46
2	5	0.12	42	13–97
3	4	0.12	33	9–84
4	5	0.12	40	13–94
5–9	5	0.35	14	5–33
10–19	5	0.32	16	5–36
20–29	3	0.11	27	5–78
≥30	2	0.97	2.0	0.2–7.5
Total	30	2.3	13	8.7–19
Acute myeloid leukemia (ICD-10 codes C92, C93)				
0	2	0.02	132	15–476
1	5	0.03	188	60–439
2	7	0.03	267	107–554
3	2	0.03	76	8.5–273
4	0	0.03	0	0–137
5–9	1	0.05	19	0.2–104
10–19	0	0.16	0	0–23
20–29	2	0.21	9.6	1.1–35
≥30	1	1.11	0.9	0–5.0
Total	20	1.66	12.0	7.1–18

CI, confidence interval; ICD, International Classification of Diseases, 10th Revision; SIR, standardized incidence ratio.

^aFive patients with unclassified leukemia were excluded.

persons with Down syndrome. The overall cancer risk in people with Down syndrome is thus very dependent of the ages of participants in the cohort studied.

The pattern of cancer among children with Down syndrome is unique: more than 95% is acute leukemia. A case of retinoblastoma was the only nonhematologic tumor identified among children younger than 15 years of age in this study, confirming the paucity of embryonic tumors such as neuroblastoma, Wilms tumor,¹¹ and medulloblastoma.¹²

The risk of leukemia is very high among children with Down syndrome younger than 5 years of age, with an SIR of 27 for ALL and 114 for acute myeloid leukemia. The risk for leukemia, especially ALL, remains elevated until 30 years of age. The high risk of acute leukemia in young children with Down syndrome is unexplained, although multiple genes on chromosome 21 might be involved.¹³ It was recently shown that trisomy 21 leads to overexpression of HMGNI, which may promote B-lineage ALL by suppressing trimethylation of lysine 27 of histone H3.¹⁴

The risk of all major groups of malignant solid tumors was decreased with the exception of testicular cancer. The risk of solid tumors was significantly reduced for men and women over 40 years of age; among the oldest age groups the cancer incidence was only 25% of that seen in the general population. Accelerated aging—for example, in the brain,¹⁵ hematopoietic cells,¹⁶ and skin¹⁷—in persons with Down syndrome might suggest an increased incidence of cancer, but the opposite was observed. The risk of therapy-related cancer is also decreased in persons with Down syndrome.³ The increased rate of apoptosis in cells with trisomy 21¹⁸ might mean that cell death is a more common response to DNA damage, thus reducing the risk of cancer.¹⁶

In contrast to other solid tumors, testicular tumors occurred three times more often than expected in men with Down syndrome, similar to the three- to fivefold increased risk of testicular cancer found in other studies.^{6,7,19–21} Testicular microlithiasis (asymptomatic calcification in the seminiferous tubules) and cryptorchidism (undescended testes), which both occur with increased frequency in Down syndrome and are associated

with an increased risk of testicular cancer,^{22–24} might contribute to the increased incidence of testicular cancer. However, cryptorchidism alone cannot explain the increased risk since it is observed in less than 20% of testicular tumors among persons with Down syndrome.²⁵ Acquired gain of chromosome 21 material occurs in most cases of seminoma,²⁶ and chromosome 21 gene dosage may play a direct pathogenetic role in men with Down syndrome.

We observed an SIR of 1.0 for ovarian cancer, as was the case in the study from Finland.⁷ Other studies found a non-significant increase in the occurrence of ovarian cancers^{19,20} or decreased mortality from ovarian cancer among women with Down syndrome.⁶ We conclude that the risk of ovarian cancer is probably comparable to that in the general population.

Health behaviors associated with increased risk of cancer (e.g., smoking and sun exposure) might be less common in persons with Down syndrome compared with the general population. Some smoking-related cancers, such as lung cancer, were decreased to only 10% of expected, but the risk of other smoking-related cancers, such as stomach and bladder tumors, were not decreased in our cohort. The absence of cervical cancer might be related to decreased sexual activity—most women with Down syndrome are nulliparous²⁷ despite being fertile.

Many adult men and women with Down syndrome are overweight and have low physical activity,^{28,29} but the increased risk of cancers of the breast, uterus, colon, intestine, liver, gallbladder, and kidney associated with high body mass index in the general population³⁰ seems to be counterbalanced by protective factors in Down syndrome.

Nulliparity and obesity are associated with breast cancer in older women,³¹ but, despite both factors being present in the vast majority of women with Down syndrome,^{27,28} the occurrence of breast cancer is only 10% of the expected. Early menopause is more common in Down syndrome and might contribute to a reduced risk of breast cancer.³² The three cases of breast cancer in women with Down syndrome all occurred at relatively young ages (31, 47, and 55 years), which may indicate less influence from lifestyle factors. We do not have any information on familial genetic predisposition to breast cancer in the cohort.

Chromosome 21 contains more than 200 genes, and several of these seem to be involved in carcinogenesis.¹⁶ Data from a mouse model of Down syndrome provide evidence for a tumor repressor effect of the chromosome 21 orthologous gene *Ets2*.³³ Based on studies of mouse and human cells, the gene *DYRK1A* on chromosome 21 may possess both tumor-suppressor and leukemogenic properties.³⁴

The reduced risk of solid tumors and benign vascular tumors in Down syndrome³⁵ may be explained by endogenous antiangiogenic regulators derived from genes on chromosome 21. Endostatin encoded by the *COL18A1* gene at 21q22.3 is a potent angiogenesis inhibitor, and the serum concentration of endostatin is significantly higher in Down syndrome.³⁶ Another chromosome 21–derived protein

encoded by *DSCR1* suppresses vascular endothelial growth factor–mediated angiogenesis and may also be involved in protection against solid tumors.^{37,38}

This study has several strengths. It is based on a large unselected population of persons with Down syndrome, with a comparison with cancer rates in the sex- and age-matched general Danish population from which the Down syndrome cohort was drawn. The large number of persons with Down syndrome and years of observation allow for precise estimates of the incidence of cancer. Use of the Danish Cytogenetic Registry means that ascertainment of persons with Down syndrome diagnosed since 1961 is likely to be complete. In addition, the use of these data allows analysis of the cancer risk by karyotype (standard trisomy 21, Robertsonian translocation, or mosaicism). The cohort data were linked to the Danish Cancer Registry, a database that is believed to be complete and to have a high degree of accuracy regarding type of tumor and ascertainment.

The study also has several limitations. The findings we observed could be due to cancer being less commonly diagnosed among persons with Down syndrome, rather than decreased incidence. The health-care system in Denmark is public and paid for by taxes, so lack of access is unlikely to explain the lower incidence of cancer. It is possible, however, that persons with Down syndrome might be less likely to report symptoms or to participate in cancer screening programs; thus, cancer might be diagnosed later.³⁹ However, the finding of lower mortality from solid tumors among people with Down syndrome in other studies makes this explanation less likely.⁶ Another limitation is that information on cancer risk factors (e.g., tobacco use and sexual activity) was not available. Finally, the study was conducted in Denmark, which has a rather homogeneous Northern European population and might not be generalizable to other populations.

People with Down syndrome pose a paradox with accelerated aging but also a lower incidence of solid tumors compared with the age-matched general population. Better understanding of the decreased risk for most solid tumors among people with Down syndrome may lead to altered screening strategies for this group and may be helpful in identifying new methods for cancer prevention and therapy for the general population.

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DISCLOSURE

The authors declare no conflict of interest.

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