Characteristics in Youth Predictive of Adult-Onset Malignant Lymphomas, Melanomas, and Leukemias: *Brief Communication* [1,2,3]

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ABSTRACT—**College** health records of 50,000 male alumni of **Harvard** University (Cambridge, Mass.) and the University of **Pennsylvania** (Philadelphia, Pa.) were examined for **characteristics that** were predictive of risk of fatal lymphaden, blood, and **skin cancers.** Among these alumni, 45 men with Hodgkin's disease, **89** with non-Hodgkin's malignant lymphoma, 45 with malig**nant melanoma, 27** with lymphatic leukemia, 41 with myeloid **leukemia,** and **30** with other and unspecified leukemia died from **their disease** in **1.71** million person-years of observation. Men **grouped** according to the type of cancers they had, identified **from** death certificates, were contrasted with four times as many **surviving** classmates in terms of potential predictive character**istics.** Relative risks of these six cancers may be grouped by **predictive** characteristics in youth as follows: **1)** History of **common** contagious diseases of childhood was predictive of a lower **risk of** Hodgkin's disease and lymphatic leukemia, but varicella **indicated** increased risk of other malignant lymphomas and **unspecified** leukemia. **2)** Tonsillectomy was associated with **higher** risk of unspecified leukemia. **3)** Obesity was a predictive **factor** of excess risk of Hodgkin's disease, whereas leanness **was** associated with higher risk of other lymphomas. 4) Both **coffee** drinking and heavy cigarette smoking pointed to higher **risk** of Hodgkin's disease, myeloid leukemia, and lymphatic leukemia. **5)** Outdoor environmental exposure indicated in**creased** risk of malignant melanoma. **In** the tendencies noted, Hodgkin's disease and lymphatic leukemia had parallel **predictive** factors that were opposite to those of non-Hodgkin's malig**nant** lymphoma, myeloid leukemia, and unspecified leukemias. **Malignant** melanoma shared none of these predictive character**istics.** These findings are presented as clues deserving further **exploration** for any etiologic significance they may hold for **lymphaden** and blood **cancers.**—J Natl Cancer **Inst** 60: **89–92, 1978.**

Characteristics recorded at college physical examinations of 50,000 male former students from Harvard University (Cambridge, Mass.) and the University of Pennsylvania (Philadelphia, Pa.) were reviewed for their relationship to risk of fatal lymphaden, blood, and skin cancers. Students from a 35-year period were traced for 1.71 million person-years of observation during which 277 deaths from these cancers were identified. Hypotheses of causation of Hodgkin's disease *(1)* were tested against non-Hodgkin's malignant lymphoma, malignant melanoma, lymphatic leukemia, myeloid leukemia, and other and unspecified leukemia. Relative risks of these cancers were computed for potential predictive characteristics in youth: history of contagions, familial tendencies, physical attributes, personal traits, and societal influences. Our purpose was to identify leads for subsequent study of these cancers.

METHODS

Physical examinations were performed on study subjects on entering Harvard University, 1916–50, or while attending the University of Pennsylvania in 1931–40. Characteristics compiled from these records were assessed as potential predictive factors (2, *3).* Less than 1% of the 50,000 men has been lost to follow-up observation by alumni offices without notification of deaths.[7] Causes of death were identified and classified from official death certificates with the use of the coding rules of the Seventh Revision of the ICD (1957) *(4).*

In this review, **4** control subjects for each site-specific cancer decedent were chosen randomly from classmates born in the same year and known to survive the decedent. Relative risk estimates for each cancer were computed for 17 characteristics previously studied for their relationship to risk of fatal Hodgkin's disease *(1)* and **2** additional characteristics suspected as precursors of skin cancer *(5).* **A** method of matched set analysis was used *(6–8).* Statistical probability values are quoted for two-tailed tests.

Due to the bimodal structure of age-specific death rates for Hodgkin's disease *(1),* relative risk estimates for predictive characteristics were examined separately for men younger and older than 45 years of age. Inasmuch as no differences were found, 'results were presented-for these decedents as a group. Similarities in the predictive characteristics and relative risk estimates of reticulum cell sarcomas, lymphosarcomas, multiple myelomas, and other non-Hodgkin's lymphomas permitted combination of these specific entities into a single group, "non-Hodgkin's lymphomas," as well.

RESULTS

In an earlier report *(1),* we concluded that the risk of

ABBREVIATION USED: ICD = International Classification of Disease.

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[7] For example, as of the summer of 1975. mailing addresses were unavailable for only 206 (0.62%) of 33,512 surviving Harvard University men who matriculated in 1916–30. Since Harvard University often receives notification upon the death of these men, the follow-up status of many of them ultimately becomes known.

developing Hodgkin's disease was decreased among subjects in this-population who had experienced common contagious diseases of childhood before entering college and was increased among those in the population who had a history of early parental death, especially from cancer, who were obese, or who were heavy cigarette smokers or coffee drinkers.

We had fcund no relationship between case clustering, a history of tonsillectomy, or sibship status and risk of Hodgkin's disease, though others had reported such a relationship (*9,10*).

We have tested similar hypotheses of causation for ocher lymphaden, blood, and skin cancers, together with hypotheses that might implicate exposure to sunlight (outdoor work, physical activity, and geographic origin), and present these findings in tables 1 and 2. The cancers shown are Hodgkin's disease (ICD #201), other lymphomas (ICD #200, 202, 203, and 205), malignant melanoma of the skin (#190), lymphatic leukemias (#204.0), myeloid leukemias (#204.1), and other and unspecified leukemias (#204.2, 204.3 and 204.4). In this series the mean ages at death from these cancers, respectively, were 45.3, 50.0, 48.2, 54.5, 49.2, and 47.2 years.

Neither age at onset of infectious diseases, urban versus rural origin, public versus private secondary schooling, nor socioeconomic status indicators distinguished the cancer patients from the controls. Unlike Hodgkin's disease, none of the other cancers showed evidence of bimodal, age-specific incidence. No clustering of any cancers was found in relation to college class, geographic origin, athletic status, sibship, or other circumstances potentiating transfer of infectious agents. None of the cancers, except Hodgkin's disease and some tendency in lymphatic leukemia, was found ciated with early death of a parent or familial histo cancer.

Other characteristics predictive of Hodgkin's dise (45 men) included failure of men to contract ear common contagious diseases before admission to colle (especially pertussis, scarlet fever, and varicella), ob sity, heavy cigarette smoking, and coffee drinking. Th death rate for Hodgkin's disease was 2.6 per 100,00 person-years of observation.

There were 89 fatal cases of non-Hodgkin's dise lymphomas (reticulum cell sarcoma, 21; lymphosar coma, 34; multiple myeloma, 15; and others, 19), whic gave a death rate of 5.2 per 100,000 person-years o observation. A higher risk of these lymphomas w found among college men having a greater frequen of early varicella; this finding was quite the reverse o the experience found with Hodgkin's disease. The de ficiency of other contagious diseases of childhood found predictive of Hodgkin's disease, showed no re tionship to the non-Hodgkin's lymphomas. Unlike t relative risk for Hodgkin's disease, the risks of the other lymphomas tended to be higher for each sub who had had a tonsillectomy. Obesity was predictive Hodgkin's disease, but for other lymphomas, whic the relative risk for a ponderal index of less than 13 was 0.5, leanness was a predisposing factor. Men who died from these other lymphomas tended to be engage less often in outside remunerative work during the youth and were more apt to have been coffee drinker than were their classmates.

Malignant melanoma of the skin was also studi because it was presumed to have an etiology differe from that of lymphaden and blood cancers. A total

TABLE 1.—*Characteristics recorded at college physical examination for men who later died from Hodgkin's diseuse, other lymphomas, malignant melanoma, and for their respective controls*

Characteristic	Hodgkin's disease				Non-Hodgkin's lymphomas				Malignant melanoma			
	Frequency of characteristic; %		Relative risk	P	Frequency of characteristic, %		Relative risk	P	Frequency of characteristic, %		Relative risk	P
	Of 180 controls	Of 45 decedents			Of 356 controls	Of 89 decedents			Of 180 controls	Of 45 decedents		
History of:												
Pertussis	66.9	48.8	0.5	0.04	57.5	53.4	0.9	0.50	61.8	63.6	1.0	0.9
Scarlet fever	24.6	11.4	0.4	0.07	17.4	15.9	0.9	0.77	14.0	13.6	1.0	0.9
Diphtheria	2.8	2.3	0.8	0.83	6.3	9.1	1.5	0.36	7.9	4.5	0.5	0.4
Measles (rubeola)	84.7	81.4	0.8	0.52	85.6	80.5	0.7	0.29	87.5	90.9	1.5	0.5
Varicella	68.8	54.8	0.6	0.13	59.5	71.6	1.7	0.05	63.3	72.7	1.6	0.2
Mumps	56.9	51.2	0.7	0.44	43.9	42.9	0.9	0.54	44.0	47.7	1.3	0.4
Rubella	58.3	50.0	0.8	0.78	45.7	66.7	2.1	0.30	36.8	40.0	1.1	0.8
Influenza	25.2	17.2	0.6	0.30	19.2	17.6	1.0	0.90	23.1	15.2	0.6	0.3
A parent dead	10.2	25.0	3.3	0.02	18.4	12.5	0.6	0.18	16.9	17.8	1.1	0.8
Only-child status	15.5	20.5	1.4	0.46	15.2	13.6	0.8	0.62	10.8	13.3	1.3	0.6
2+ siblings	48.9	43.2	0.9	0.78	55.0	52.3	0.9	0.54	58.0	62.2	1.3	0.5
Tonsillectomy	64.4	63.6	0.9	0.84	61.7	70.9	1.5	0.12	65.5	68.2	1.1	0.7
Ponderal index, <12.9	24.3	37.8	1.9	0.06	25.9	14.9	0.5	0.04	19.8	25.0	1.3	0.5
Cigarette smoker	29.7	35.0	1.4	0.48	26.8	34.2	1.4	0.20	28.8	35.0	1.4	0.3
10+ per day	7.7	17.9	2.8	0.06	10.1	6.5	0.6	0.33	10.6	10.3	0.8	0.6
Coffee drinker	47.2	65.2	2.5	0.07	53.1	63.3	1.6	0.14	51.0	57.7	1.3	0.5
Exercise, <5 hr/wk	41.4	33.3	0.8	0.63	40.6	41.4	1.0	0.97	47.9	42.9	1.0	0.9
Outside remunerative work	13.3	11.8	1.2	0.73	15.8	10.4	0.5	0.14	9.5	27.3	3.9	0.0
New England origin	35.8	47.2	1.7	0.21	33.6	23.0	0.6	0.14	48.1	37.1	0.5	0.1

TABLE 2.—*Characteristics* recorded at *college* physical examination *for* men *who* later died *from* myeloid, lymphatic, or other and unspecified leukemia, and for their respective controls

Characteristic	Lymphatic leukemia				Myeloid leukemia				Other and unspecified leukemia			
	Frequency of characteristic, %		Relative risk	P	Frequency of characteristic, %		Relative risk	P	Frequency of characteristic, %		Relative risk	P
	Of 108 controls	Of 27 decedents			Of 164 controls	Of 41 decedents			Of 120 controls	Of 30 decedents		
History of:												
Pertussis	68.9	34.6	0.2	<0.01	63.0	53.7	0.7	0.26	69.8	66.7	1.3	0.51
Scarlet fever	19.6	11.5	0.6	0.36	13.6	17.1	1.3	0.54	12.5	13.3	1.1	0.90
Diphtheria	2.8	7.7	2.7	0.26	4.9	7.3	1.5	0.55	5.9	6.7	1.1	0.90
Measles (rubeola)	90.7	80.8	0.4	0.16	84.0	87.8	1.4	0.54	89.1	90.0	1.1	0.87
Varicella	68.2	38.5	0.3	0.01	59.9	51.2	0.8	0.46	62.2	90.0	5.5	<0.01
Mumps	57.1	53.8	0.9	0.90	53.2	51.3	0.9	0.84	42.4	34.5	0.7	0.38
Rubella	50.0	100.0	—	—	33.3	33.3	0.8	0.81	20.0	0.0	—	—
Influenza	17.7	17.4	1.1	0.90	23.4	8.8	0.4	0.13	22.1	23.1	1.0	1.00
A parent dead	16.0	26.9	1.8	0.24	15.4	20.0	1.4	0.47	16.1	16.7	-1.1	0.91
Only-child status	12.1	4.0	0.3	0.26	9.4	15.0	1.8	0.30	12.5	13.3	1.1	0.90
2+ siblings	55.1	64.0	1.3	0.56	70.6	62.5	0.7	0.27	55.0	46.7	0.7	0.40
Tonsillectomy	59.4	65.4	1.2	0.65	55.7	62.5	1.2	0.60	64.1	89.3	4.7	0.01
Ponderal index, <12.9	24.1	26.9	1.2	0.76	29.0	15.0	0.4	0.08	28.0	31.0	1.1	0.77
Cigarette smoker	30.5	34.8	1.3	0.57	30.9	50.0	2.4	0.03	24.3	29.6	1.3	0.63
10+ per day	9.7	17.4	2.7	0.17	7.0	19.4	3.6	0.03	6.4	3.8	0.6	0.65
Coffee drinker	46.3	66.7	2.7	0.06	49.0	66.7	3.2	0.02	57.0	52.6	0.8	0.73
Exercise, <5 hr/wk	34.7	45.0	1.6	0.48	31.9	50.0	2.4	0.16	47.1	56.3	1.9	0.35
Outside remunerative work	9.5	7.7	1.0	1.00	11.4	20.0	1.8	0.27	13.0	9.1	1.0	0.97
New England origin	40.9	44.4	1.3	0.69	46.3	51.9	1.2	0.66	40.0	40.0	0.8	0.82

45 men died from malignant melanoma, an incidence rate of 2.6 per 100,000 person-years of observation. Of the potential predictive characteristics examined, only outside (presumably outdoor daytime) employment before college was significantly associated with malignant melanoma: Outdoor workers had a relative risk 3.9 Limes greater than that of men who did not report outdoor work. In contrast to students who came from other areas, students from New England had only half the risk of malignant melanoma, but the difference was not statistically significant.

The 27 lymphatic leukemias (incidence rate of 1.6/100,000 person-years of observation) were notably similar to Hodgkin's disease in predictive characteristics of the subjects. Risks were significantly lower for men who had experienced common contagious diseases of childhood before entering college, particularly pertussis and varicella. The relative risk for heavy cigarette smoking and for coffee drinking was 2.7, another characteristic parallel to that seen with Hodgkin's disease patient s.

The 41 men with myeloid leukemia (an incidence rate of 2.4/100,000 person-years of observation) did not have the predictive factor of early history of contagion. As was found for students who later developed non-Hodgkin's lymphomas, lean rather than obese college students tended to develop these leukemias. The relative risk of myeloid leukemia was 2.4 for cigarette smokers, 3.6 for heavy cigarette smokers, and 3.2 for drinkers of any amount of coffee; all tendencies were significantly greater than unity.

We found 30 other and unspecified leukemias (acute, 18; monocytic, j; and unspecified. 7) that gave an incidence rate of 1.7 per 100,000 person-years of observation. An early history of varicella was associated strongly with these leukemias (relative risk, 5.5), as was a history of tonsillectomy (relative risk, 4.7). In such predictive relationships these leukemias are parterned after the non-Hodgkin's lymphomas. None of the other characteristics studied presage any of this medley of leukemias.

DISCUSSION

Whether or not the data reviewed here identify causal relationships, the differences in predictive characteristics between Hodgkin's disease and other malignant lymphomas do suggest differing etiologies. By the same token, similarities in predictive factors in youths who later develop Hodgkin's disease or lymphatic leukemias could signify common etiologies as could similar predictive factors in youths who later develop non-Hodgkin's malignant lymphoma, myeloid leukemia, or unclassified leukemia. Malignant melanoma shares no host predictive characteristics with the other cancers and seems to result from another cause.

Suggested hypotheses of causation for Hodgkin's disease, based primarily on history of reduced frequencies of childhood contagions by the time the youth enters college, are as follows: 1) Birth cohorts ivith inadequate immune mechanisms either succumbed to or escaped childhood infections, leaving the survivors predisposed to Hodgkin's disease whether or not Hodgkin's disease is of infectious origin. 2) Originally normal or abnormal immune mechanisms were inadequately challenged by early childhood infections and so were not precondi-

tioned to withstand the assault of Hodgkin's disease later in life. **3)** Hyperimmune mechanisms aborted clinical attacks of childhood contagions (other than the ubiquitous measles) and fostered an autoimmune phenomenon leading to Hodgkin's disease. Any of these hypotheses fit the observed inverse relationship of childhood contagious diseases and subsequent risk of Hodgkin's disease and are equally applicable to lymphatic leukemia patients who have a similar array of predictive characteristics.

The observation that a predictive factor of Hodgkin's disease is reversed for non-Hodgkin's malignant lymphomas, i.e., occurrence of childhood infections (notably varicella), invites for other lymphomas some adaptations of the Hodgkin's hypotheses of causation: 1) An inadequate immune system might fail to contend with the effects of varicella infection, leading to development of non-Hodgkin's maligant lymphoma. **2)** The varicella itself may be a slow-acting virus that directly causes lymphoma. **3)** The varicella infection may have altered or sensitized the lymphatic system by a single or repeated process that renders, the subject receptive to development of the lymphoma either as a subsequent infection or as an autoimmune phenomenon.

The observation that childhood varicella is predictive of non-Hodgkin's malignant lymphoma and unclassified leukemia has some parallel to the observation that a history of tonsillectomy also tends to be predictive of these cancers. It is likely that the increase in tonsillectomies accompanies the increase in infectious diseases of childhood.

At this point, the aforementioned hypotheses are merely leads in the search for causation, though in several animal models evidence that autoimmunity may lead to certain lymphoreticular diseases has been found (*11*). Others have reported associations between influenza or varicella and the subsequent development of leukemias and lymphomas (*12-14*). Contrary to our findings, one group of investigators found an association between varicella and lymphatic leukemia (*12*), another between varicella and unspecified and lymphatic leukemias (*13*), and a third between influenza and lymphatic–hematopoietic neoplasms (*14*). These associations have been based, however, on in utero infection with varicella or influenza rather than on childhood infection, and the end points of interest have been childhood leukemias and lymphomas rather than adult lymphaden and blood cancers.

Patients with Hodgkin's disease and non-Hodgkin's malignant lymphomas have opposing-predictive factors in obesity and leanness that occur during youth. These physical characteristics would appear to have a secondary relationship to these cancers, as contrasted to the potentially more direct role of other predictive factors such as childhood contagions. Nevertheless, these extremes of weight for height differ significantly from the norms of classmate controls and deserve to be kept in account.

The patterns of associations involving heavy cigarette smoking and collegiate coffee drinking in these data do not readily suggest causal hypotheses. Unless smoking and coffee drinking are somehow linked with autoimmunity or sensitizing processes, the roles of these predictive characteristics are more likely those of widely implicated secondary characteristics.

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