MORTALITY FROM CARCINOMA OF THE UTERUS AN INTERNATIONAL COHORT STUDY

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In a previous paper (Hill and Adelstein, 1967) it was shown that mortality rates from cancer of the cervix uteri in England and Wales have been declining in successive generations of women, with the striking exception of those women who were born round about 1911 to 1924 who had higher rates of mortality than those who were born before and after them. It was suggested that this pattern, taken in conjunction with other evidence, was consistent with the hypothesis that infection was a cause and that the added infection had come about as a result of war-time disturbances of customary sexual partnerships. The point was made that the trends shown in the cohort study of cancer of the uterine cervix would be present in the same way if the study considered the totality of uterine cancers, since cervical tumours comprise a high proportion of the total. In the present study we use the same arguments to analyse the figures for mortality from cancer of the uterus in 20 countries.

MATERIALS AND METHODS

Annual figures of population and of deaths from cancer of the uterus from 20 countries have been taken from publications of WHO and the Registrars General of England and Wales and Scotland. Using the method described by Case (1956) as quinary-quinquennial, the figures are aggregated

for periods of five years for each five-year age group. Table I shows the figures for England and Wales from 1949 to 1968; the rates for each successive 'cohort' are shown in a series of rows.

In order to save space in Table II the figures for each country are shown in three continuous rows instead of the customary stepwise progression for successive cohorts as in Table I. Mortality figures for successive age groupings of each cohort appear in the diagonals instead of in rows. The figures for each particular cohort are indicated by a stepwise line identified, at the bottom of the table, by the middle year of the period during which the women were born. Reading the figures in a column, say, for the Netherlands at ages 55-59, note that the three rates 371, 325, and 290, which refer to women born in three different cohorts, round about 1894, 1899, and 1904 respectively, show a progressive decline. However, the two figures on the diagonal of the cohort with birth year 1914 are each *higher* than that of the corresponding age-group above, i.e., in the previous cohort (204 and 257 as against 175 and 235).

RESULTS AND DISCUSSION

The interpretation of these 'cohort mortality' figures must take into account a number of technical problems: first, the figures are for cancers of

TABLE I
MORTALITY FROM CARCINOMA OF UTERUS, 1949-68, ENGLAND AND WALES, SUCCESSIVE COHORTS, QUINARY-QUINQUENNIAL METHOD

Central Date of Birth	Death-rate per Million in Women Aged									
	25-29	30-34	35-39	40-44	45-49	50-54	55-59	60-64	65-69	70-74
1879										582
1884									549	558
1889								499	488	521
1894							433	440	463	493
1899						308	360	407	429	
1904					199	264	301	354		
1909				118	183	238	298			
1914			63	119	200	269				
1919		34	75	149	217					
1924	12	41	81	141						
1929	12	27	58							
1934	11	18								
1939	8									

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TABLE II
MORTALITY FROM CARCINOMA UTERUS, VARIOUS COUNTRIES 1949-63,
SWEDEN 1951-65, QUINARY-QUINQUENNIAL METHOD

Country	Date of Death	Age Group									
		25-	30-	35-	40-	45-	50-	55-	60-	65-	70-
Norway	1949-53	17	52	106	159	173	311	330	396	333	446
	1954-58	29	73	111	139	240	272	373	369	322	369
	1959-63	14	41	118	146	198	188	246	351	362	407
New Zealand	1949-53	3	24	55	122	195	340	474	495	573	606
	1954-58	6	20	86	98	147	283	304	478	462	618
	1959-63	3	43	74	93	212	194	342	364	526	524
Australia	1949-53	12	37	61	119	186	289	383	481	498	614
	1954-58	15	28	53	106	171	257	340	407	540	558
	1959-63	8	25	75	121	166	207	283	345	431	515
Eire	1949-53	14	34	59	88	215	258	316	328	355	384
	1954-58	7	32	55	114	167	316	296	367	393	425
	1959-63	—	39	71	75	139	228	227	310	276	441
E. & W.	1949-53	12	34	63	118	199	308	433	499	549	582
	1954-58	12	41	75	119	183	264	360	440	488	558
	1959-63	11	27	81	149	200	238	301	407	463	521
Sweden	1951-55	23	67	94	130	193	273	331	389	426	477
	1956-60	27	58	120	171	198	248	304	380	426	477
	1961-65	16	37	104	146	221	246	325	340	404	469
Netherlands	1949-53	18	34	64	128	175	322	371	407	452	599
	1954-58	12	57	111	140	204	235	325	404	404	504
	1959-63	11	39	89	142	212	257	290	370	436	449
Canada	1949-53	22	63	116	206	325	364	457	546	600	702
	1954-58	25	54	99	170	259	319	390	504	571	591
	1959-63	18	43	102	151	212	263	353	461	484	554
N. Ireland	1949-53	23	61	90	167	268	397	494	419	516	509
	1954-58	4	50	77	140	206	246	328	385	351	476
	1959-63	4	22	60	171	172	272	295	343	372	345
Scotland	1949-53	24	50	106	167	241	328	436	481	534	619
	1954-58	12	93	115	174	266	318	386	495	483	538
	1959-63	13	98	98	179	258	292	298	390	470	470
Cohort birth date		1934 1929 1924 1919 1914 1909 1904 1899 1894 1889 1884 1879									

cont.

Table II—continued

Finland	1949-53	13	45	100	102	239	343	462	518	560	640		
	1954-58	10	41	111	165	224	310	404	390	440	498		
	1959-63	8	30	81	141	183	296	363	387	474	579		
U.S.A.	1949-53	30	71	148	239	346	446	529	621	724	803		
	1954-58	27	64	122	190	274	371	449	544	655	690		
	1959-63	22	55	104	161	222	296	373	479	574	630		
Switzerland	1949-53	16	40	99	126	200	323	429	497	594	708		
	1954-58	14	38	75	125	225	314	430	532	693	763		
	1959-63	13	29	76	130	187	303	361	480	616	727		
S. Africa	1949-53	32	62	110	175	297	454	525	548	653	772		
	1954-58	15	26	101	170	220	345	435	595	595	693		
	1959-63	15	43	66	161	218	307	375	550	612	738		
France	1949-53	14	46	92	166	248	337	421	488	554	622		
	1954-58	13	44	99	164	246	325	403	459	533	575		
	1959-63	7	33	88	160	242	316	356	438	509	574		
W. Germany	1949-53	36	96	176	251	362	476	559	626	716	841		
	1954-58	24	73	148	226	287	345	400	450	488	563		
	1959-63	17	55	130	215	295	328	365	417	471	498		
Denmark	1949-53	45	101	179	303	397	461	504	589	634	709		
	1954-58	54	124	191	285	382	446	530	682	642	733		
	1959-63	38	115	227	304	364	429	522	637	751	762		
Japan	1949-53	26	83	211	393	593	714	768	816	833	723		
	1954-58	24	51	123	262	429	570	631	692	735	746		
	1959-63	24	47	94	183	320	445	537	617	667	690		
Austria	1949-53	62	109	227	336	474	578	639	727	761	1034		
	1954-58	36	117	202	328	465	536	654	685	757	827		
	1959-63	27	88	162	266	458	474	586	660	767	804		
Chile	1949-53	56	163	270	378	459	547	613	686	781	888		
	1954-58	55	130	211	348	486	492	684	651	903	823		
	1959-63	39	118	182	305	434	507	632	644	847	900		
Cohort birth date		1934	1929	1924	1919	1914	1909	1904	1899	1894	1889	1884	1879

all the uterus, whether cervix or other (with the assumption that the underlying trends depend on changes in the number of cases of cervical cancer); second, the method of aggregating the published annual mortality involves overlap between adjacent cohorts, thus weakening any underlying cohort effects; third, the number of deaths, especially in the younger ages and in countries with small numbers of people, may be relatively few, thus allowing unexplained random fluctuations or 'noise'. These three technical factors together must result in a weakening of any underlying statistical trends which we are discussing.

There are well-known examples of stability in cohort trends, in the sense that the rates of mortality of any particular generation maintain the same pattern of relationships, age group by age group, to other generations. For example, Frost (1939) showed how, in many countries, mortality from pulmonary tuberculosis in each generation rose to a peak in young adults and declined in the older persons; and, since these mortality rates in every age group were declining over time this cohort pattern was completely obscured in the age-specific rates of any particular year taken in isolation, in which case the rates rise regularly with age since the young persons of the present generation are compared with the aged of previous generations. Similarly, it is well known that the cohort pattern of mortality from lung cancer—in this case the rate has been increasing in successive generations—shows that the mortality of each generation maintains a stable relationship to that of other generations; in other words, it may be said that once the relative position of a mortality rate of young persons is known the trend of rates for the entire span of life can be predicted in its general configuration and in its relationship to mortality of other generations.

Such examples of stable relationships of mortality rates between generations are understandable if events at a particular age lead to consequences measured by subsequent mortality. In the case of tuberculosis these events occur at very young ages—an interplay between infection and immune responses; also lung cancer follows predictably from habits of smoking relatively early in life.

The figures for cancer of the uterus in the countries selected do not display such a clear picture of stability among cohort rates in every country. But this is to be expected by the very nature of the hypothesis and the paucity of data. Perhaps it is the more surprising that the trends are shown at all. In general, in each of these countries the rates in successive generations have been falling. Overlying this falling trend three types of pattern may be

discerned; in some countries the falling trend is clearly reversed by the figures of particular cohorts, and continues to fall in subsequent cohorts (this pattern is similar to that shown for England and Wales); in some countries there is a strong suggestion of a similar pattern but it is not so clear; in the remaining countries the falling trend in successive cohorts is uninterrupted.

Table III lists the countries (in order of the latest published mortality rates at age 50–54). In the second column are listed the birth years of these cohorts—identified by middle year of a five-year span—in which mortality figures completely reverse the trend of the cohort rates falling over time; that is to say the two figures which can be compared with those of the previous cohort are both higher. For example, in Scotland, the figures for the cohort born around 1919 are both *higher* than those of the cohort born in 1914. Returning to Table II, for Scotland the generation born around 1919 when they reached age 35–39 had a mortality rate of 115 as compared with 106 for the previous cohort born around 1914. Similarly, when the women born around 1919 reached 40–45 years of age their rate of mortality, 179, was again higher than that of the previous cohort—174.

In the third column of Table III are shown those cohorts for whom only *one* of the two figures com-

TABLE III
COHORT MORTALITY FROM CANCER OF UTERUS IN VARIOUS COUNTRIES, SHOWING COHORTS (BY CENTRAL YEAR OF BIRTH) WITH (i) COMPLETE REVERSAL OF DECLINING TREND, AND (ii) PARTIAL REVERSAL OF TREND

Country	Cohorts (Birth Date) showing		Mortality Rate Age 50–54 (latest reported)
	(i) Complete Reversal	(ii) Partial Reversal	
Norway	1924, 1919	1929, 1909, 1899, 1894, 1889	188
New Zealand	1929	1919, 1914, 1904, 1894, 1884	194
Australia		1929, 1924, 1919, 1889	207
Eire	1889	1929, 1924, 1914, 1904, 1894	
England and Wales	1924, 1919, 1914		238
Sweden	1914	1929, 1919, 1909, 1904	246
Netherlands	1919, 1914, 1909	1924, 1894	257
Canada		1929, 1924	263
N. Ireland		1919, 1909, 1894	272
Scotland	1919	1934, 1929, 1924, 1914, 1909, 1894	292
Finland		1919, 1914, 1894, 1889	296
U.S.A.			296
Switzerland		1924, 1919, 1909, 1899, 1894, 1889, 1884	303
S. Africa	1894	1929, 1889	307
France		1919	316
W. Germany		1914	328
Denmark	1924, 1919, 1894, 1889	1929, 1899, 1884	429
Japan			445
Austria		1924, 1899, 1894	474
Chile	1909, 1889	1899	507

parable with those of the preceding cohort breaks the declining trend, i.e., is larger. Interpretation of this column needs to take into account the factors discussed, 'noise' and overlap. However, it is interesting that the cohorts frequently listed in this column are the same as those in the preceding column, namely, those born between 1911 and 1924, and also those born round about 1889-99.

Considering all the data, in a number of countries there is clear evidence that the declining mortality rate (present in all these countries) was interrupted, the reversal having a typical 'cohort' quality affecting the generation who were in early womanhood during the years of the second world war. These countries are England and Wales, Scotland, Netherlands, Denmark, Norway and Sweden (in Europe), and Chile and New Zealand. In each case the data for the most recent cohorts suggest, sometimes strongly, that the downward trend has become re-established. Also in some countries a similar pattern (of increased mortality) is shown for the cohorts born around 1889-94, the women who would have been young adults during the period of the first world war. Beside those countries in which there is a clear reversal of falling cohort rates, there are a number of countries in which it may be thought that there is a similar underlying trend but it is distorted and masked by the roughness of the analysis; this 'cross-over' of cohort mortality curves is present in all the remaining countries except the U.S.A. and Japan.

As explained previously, the figures used in these tables are the mortality rates for carcinoma of the entire uterus because only these are available reliably. In our previous paper we showed that the

cohort trend under discussion in the figures for England and Wales was revealed in the figures for cancer of the uterus as well as those confined to cancer of the cervix. Recently there have become available figures for cancer of the cervix for two provinces of Canada, Saskatchewan and British Columbia, and we show them in Table IV. In both cases the trends displayed are similar to those under discussion—a falling rate for each cohort since those born in 1874, interrupted only by two cohorts; for Saskatchewan they are the cohorts born around 1899 and 1914 and in British Columbia those born around 1884 and 1909. As noted in Tables II and III for cancer of the entire uterus in Canada, this clear pattern was not revealed. Thus in the case of Canada either our method of using figures for the uterus was not sufficiently sensitive to show the underlying trend for cervical cancer, or the pattern for all Canada is not the same as in these two provinces. If the first explanation is correct we would conclude that our method—using figures for the uterus—tends to underplay the cohort trend for cervical cancer, as we expected.

In our earlier paper we argued that the 'cohort' pattern in England and Wales taken with other research suggested the presence of an infective agent which was increased by the changes in customary sexual partnerships brought about by war and its aftermath, the essential alteration being towards earlier and more partners. Such a changing pattern of relationships may be thought to have occurred in many countries during and immediately after the war years, and especially in those countries with clear evidence of the cohort pattern of reversal.

Recently, there have been a number of clinical

TABLE IV
DEATHS (PER MILLION) FROM CARCINOMA CERVIX UTERI, SASKATCHEWAN
AND BRITISH COLUMBIA, 1954-68, QUINARY-QUINQUENNIAL METHOD

Province	Date of Death	Age Group											
		25-	30-	35-	40-	45-	50-	55-	60-	65-	70-	75-	80-
Saskatchewan	1954-58	28	26	68	44	106	66	146	110	191	237	321	388
	1959-63	15	21	48	65	126	59	102	150	93	181	214	103
	1964-68		39	44	72	82	108	52	122	195	104	157	369
British Columbia	1954-58	16	33	60	109	170	181	213	223	292	285	238	238
	1959-63	12	51	89	137	135	213	163	273	204	211	301	221
	1964-68		24	78	92	115	128	222	197	190	211	233	283
Cohort date of birth		1934	1929	1924	1919	1914	1909	1904	1899	1894	1889	1884	1879 1874

studies which point to an association between a virus (HSV-2) and anaplasia of the cervical mucosa, summarized in a leading article in the *British Medical Journal* of 31 October, 1970. The article says that further work is needed to distinguish between three alternatives: 'Firstly, both virus infection and cervical anaplasia may be independently related to promiscuity. Secondly, HSV-2 may grow preferentially in preneoplastic or neoplastic cervical tissue. And, thirdly, HSV-2 may be the cause of these diseases'. Whether this particular virus is the cause or not, the cohort mortality figures, shown here, suggest that an infective agent is causal, because no other explanation is available for these cohort trends.

SUMMARY

Mortality from carcinoma of the uterus in 20 countries is analysed by cohorts; in all countries rates of successive generations have been declining but the rates for certain cohorts are out of phase in many countries, most clearly in England and Wales, Scotland, Netherlands, Denmark, Norway, Sweden, New Zealand, and Chile. In two countries

—the U.S.A. and Japan—there is no suggestion of any intrusion in the falling trend. This intrusion of higher rates in particular cohorts is considered to be related to change in the customary sexual relationships brought about by the two world wars and their aftermath, and, taken with other evidence, the pattern is best explained by an infective cause of the cancer.

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