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Review

Studies of Cancer in Migrants: Rationale and Methodology

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Migrant populations comprise substantial numbers of individuals who have undergone a change in their environment, sociocultural and physical. The corresponding changes in risk for different cancers have, therefore, been widely used to infer the relative importance of environmental factors versus inherited predisposition in cancer aetiology. The uncontrolled experiment of migration also provides an indication of the possible effects of certain preventive interventions at the population level—especially with respect to diet. In the past, there has been a surprising lack of attention to analytical methods for migrant data, and we review the epidemiological methods available to best bring out the relevant differences in risk. The major sources of bias which confuse interpretation are also described. Migrant studies are classified into four groups, in a hierarchy corresponding to the amount of information which they can provide, and examples of each type are provided. Copyright © 1996 Elsevier Science Ltd

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STUDIES OF disease in migrant populations have long been popular with epidemiologists, since they offer insights into the relative importance of environment and genetic make-up in disease aetiology, by comparing disease risk in populations of similar genetic background living in different physical and social environments. Here we review the principles and methods of migrant studies, and provide a few illustrative examples, with no attempt at an exhaustive overview of results of such studies. For convenience, we refer only to international migration, and employ terms such as 'country of origin' and 'host country', although almost all of the material is equally applicable to studies of migration within one country.

PRINCIPLES OF MIGRANT STUDIES

Migrant studies may involve several types of comparison, the most basic being between disease rates in migrants and in their country of origin (populations of similar genetic background but different environment), or between rates in the migrants and the host country (populations of different genetic background living in the same environment). The differences in rates are sometimes described in terms of the degree of convergence between migrant and host population rates, or divergence between the rates in migrants and those in the country of origin.

Most epidemiology textbooks classify migrant studies as 'descriptive epidemiology', although there is little in the methods of analysis to distinguish them from 'analytical studies', as we point out below. Thus, the effect of the main variable of interest—migrant status—on cancer risk is investigated in terms of relative risk/rate ratios when person-years at risk can be estimated, or as odds ratios when they cannot. Most migrant studies make use of data sets derived from routine disease surveillance systems (cancer registration or death certification) rather than from interviews of individuals in *ad hoc* studies designed to test specific aetiological hypotheses. Hence, the variable migrant status (usually defined as birthplace), although highly reproducible and subject to little misclassification, is a proxy for a host of more proximal unmeasured 'exposures' (and genetic predispositions). Adjustment for confounding factors related to birthplace is generally limited since the variables available are usually few (sex, age, place of residence, occupation etc.). In our view, the use of routinely collected data is the distinctive characteristic of 'descriptive' epidemiology. The main advantage is convenience, the population base, and large size, with often thousands of subjects available (for example, 440 000 in one case–control study of migrants to Australia [1]). This permits risk for several different cancers to be examined in the same

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analysis. There are few *ad hoc* case–control studies in which the principal hypothesis tested is the effect of birthplace on risk (e.g. [2]); although restricted to a single cancer site, this approach permits collection of more detailed information on cases and the comparison group.

Migrants studies can only provide useful information when there is a difference in risk between the country of origin (specifically, the population from which the migrants came) and the host population. In the particular instance of the host population comprising the offspring of earlier migrants, there might well be less difference than were it genotypically quite different. Migrants from Spain and Italy might have considerable genetic similarity to the inhabitants of Argentina and Uruguay, for example, countries with populations largely of southern European descent.

Migrant studies are of most interest for those cancers for which it is difficult to attribute a large fraction to known environmental or genetic risk factors. Thus, oral cancer is so clearly linked to chewing habits that it is not surprising (or particularly helpful) to find that the persistence of the habit in populations of Indian origin explains fairly well their risk for this cancer [3]. Likewise, lung cancer is so powerfully linked to tobacco smoking that risk in migrants will be almost entirely determined by past smoking habits, and the contributions of other environmental factors—for example air pollution—will be quite impossible to evaluate in the absence of detailed knowledge of exposure to tobacco smoke. Conversely, the changes of risk experienced by migrants for cancers of the breast, large bowel, pancreas and prostate have been far more useful pointers to the relative importance of environmental factors in aetiology, and to the stage of carcinogenesis at which they may act. Migrant studies represent one of the few large-scale 'natural experiments' [4] on human populations, from which inferences can be drawn about the likely effects of dietary change—and specifically community-level dietary change—on cancer risks [5, 6].

The definition of migrant status is dependent upon the data sources used in a particular study. The most common classification is by place of birth, a relatively well-defined, unchanging attribute, likely to be comparable between the data sources being used (census, vital statistics, registration). Place of birth can also be used in the study of migrants within one country (internal migration). Citizenship or nationality is often recorded on death certificates; it is less useful than place of birth, since migrants will become naturalised to varying degrees, and there are more problems of definition (e.g. dual nationality, stateless persons). Even more difficult to define in any consistent manner are personal descriptions such as national or ethnic 'origin' or 'ancestry', whose meanings "range from a rough biological concept, through one involving the national origin of one or more of the ancestors of the person concerned, to a question of cultural affiliation with historically well-defined groups within a country" [7]. Other variables, particularly ethnic group (but also language or religion), have been widely used in comparative studies of populations of different genetic background living in similar environments (or vice versa), in a manner analogous to studies of risk by birthplace. Studies which employ a combination of ethnic group and birthplace to distinguish first-generation migrants and their offspring are much more informative than either one alone.

The term 'environment' embraces, of course, more than the physical surroundings of an individual; it also encompasses all elements of lifestyle that influence cancer risk. Thus, while certain aspects of the physical environment (e.g. air and its pollutants, water and trace elements, irradiation—solar and other forms) change abruptly on migration, other aspects of lifestyle which are related to sociocultural norms will be retained to a greater or lesser degree in the new place of residence. Examples are patterns of diet, childbearing, alcohol and tobacco consumption, sexual habits, and so on. Sociocultural factors also influence the degree of exposure to external environmental agents; thus, given that potential exposure to ultraviolet radiation from the sun is determined by geographical locality, the actual exposures will be modified by culturally defined behaviour. As a result, although migrants to countries with sunny climates, such as Israel or Australia, clearly have the same potential for exposure to ultraviolet radiation as the local population, they may be culturally more or less inclined to avoid the sun than the locally born.

There are two approaches to investigating the rate of change of risk in the migrants: the study of risk in relation to age at migration/duration of residence, and the comparison of risk in migrants and their offspring.

The study of cancer risk in relation to duration of stay in the new country, or, alternatively, according to the age at the time of migration, is feasible when information is available on the date of migration of the individuals. Provided migrants settle permanently in the host country, age at diagnosis or death is the summation of age at arrival and duration of stay, and definition of any two of these factors implies knowledge of the third. As age is in itself such a strong determinant of risk, and thus an essential factor in any analysis, there is no variability left in duration of stay after controlling for age at arrival, or vice versa; these two variables are therefore inextricably linked, unlike most other exposures, where age of first use, for example, and duration of use can be distinguished. This problem constitutes an extension of the non-identifiability property of age/period/cohort models in the study of time trends [8, 9]. A pragmatic solution is to examine each variable in turn (age/duration of stay, or age/age at arrival) to see which provides the most plausible pattern of change of risk, bearing in mind that duration of stay and age at arrival inevitably are confounded by each other.

Usually, no information is available on the extent to which migrants change their lifestyle. The variable 'duration of stay' is interpreted in terms of dose, i.e. assuming that longer periods spent in the new location imply a greater change in cumulative exposure to the relevant aetiological factors for the cancer. It might equally be interpreted in terms of the stage of carcinogenesis at which particular environmental exposures may act. Thus, a rapid change in risk following migration implies a change in exposure to a relevant factor, which acts at a fairly late stage in carcinogenesis. Alternatively, the pattern of change may suggest that a prolonged exposure is needed before risk is altered, or that the agent is only important with respect to exposures early in life. Analysis of risk by 'age at migration' may show a clear distinction, in this case, between migrants arriving as children or as adults.

Studies of cancer risk in the offspring of migrants also use time in the new environment as a proxy for 'dose'. In this instance, the populations studied have been exposed to the environment of the host country for their entire lifespan. However, it is quite likely that they retain some aspects of their parents' lifestyle (as well as their genetic makeup). Some insight into the effect of this can be gained if comparisons

based on birthplace of parents (neither, one, or both in the country of origin) are possible. These studies require that the data source used contains information on birthplace of parent(s), or ethnicity (if the migrants comprise a distinct ethnic group), or both.

Descriptive epidemiological studies using vital statistics or cancer registry data will have no information on levels of exposure (diet, tobacco, fertility, etc.). However, other data sources may be able to provide population-level data on prevalence or intensity of exposures, and permit ecological analyses of risk versus exposure according to birthplace. The opportunities for such studies are, unfortunately, limited. Although several countries perform population surveys on, for example, the distribution of smoking, drinking and dietary habits, either place of birth is not recorded or, if it is, the samples are usually too small for meaningful results to emerge for any particular group of migrants, who will usually constitute only a small fraction of the population. Occasionally, there have been special *ad hoc* surveys of migrant populations—and sometimes data from control groups in case-control studies where ethnicity or place of birth has been a major variable of interest (notably in studies of diet and cancer in Hawaii [10–12]). These may provide information on, for example, dietary habits in different migrant groups for comparison with those of the locally-born population.

BIASES IN MIGRANT STUDIES

Use of mortality data

Mortality data are normally used as a proxy for incidence (risk of disease), a perfectly valid procedure providing the ratio between mortality and incidence is constant for the groups being compared. This may not be true for international comparisons, since there are apparent differences in survival from cancer between different countries [13].

It is less clear whether there are differences in survival by birthplace within a country—surprisingly no one has investigated survival in migrants. Probably such differences that exist are related to confounding by factors such as region of residence and socioeconomic status, but if no adjustment is made for these (see *Confounding* below), they would lead to bias in interpreting mortality rates.

Data quality

Variation in the quality of data from different sources is particularly troublesome when mortality rates in one country (locally-born and migrants) are compared with those from another (country of origin). There is considerable disparity between countries in the accuracy of the coded underlying cause of death. It may relate to differences in access to diagnosis facilities, the way death certificates are completed, or the coding of underlying cause of death. The effect is to introduce spurious differences in mortality rates. Thus, if the migrant population under study moves from a country with poor certification (of all causes, or a specific cause of death) to one with more accurate recording, there will be an apparent increase in the observed rate. It is quite possible that better ascertainment of some cancers—especially those which present diagnostic difficulties—may account for the phenomenon of 'overshoot' (rates in migrants higher than host country, but country of origin rates lower), reported in several studies [14–17].

Incidence rates from cancer registries are probably more comparable between countries than mortality data. Nevertheless, incidence can be influenced by the detection of asymptomatic cancers during screening, surgery, or autopsy, and is thus related to the extent and nature of such practices. Systematic histological examination of material removed at transurethral prostectomy is responsible for the detection of many 'incidental' (non-symptomatic) cancers of the prostate in the U.S.A., and it has been suggested [18] that the incidence in Japan might be three to four times higher in the same circumstances. This would explain the apparent rapid increase in the risk of prostate cancer in Japanese migrants to the U.S.A.

Comparisons within a country are less likely to suffer from systematic biases in data quality, although they could result from the use by migrant populations of different healthcare facilities from the general population.

Bias arising from defects in data quality cannot be eliminated. It should be systematically sought for by comparison of indices such as the proportion of deaths certified with non-specific causes (senility, etc.), and cancer deaths at ill-defined sites, and the traditional quality indicators of cancer registries—percentage histologically verified and death certificate only cases, and the ratio of mortality to incidence [19].

Some cancer sites are notoriously prone to misclassification at registration or death certification. A well-known example is cancer of the uterus, for which the proportion of deaths recorded as 'uterus, unspecified' (ICD-9 179) varies enormously between countries, leading to large artefactual international differences in the death rates of cervix cancer and cancer of the corpus uteri.

A less obvious example is cancer of the large bowel, where division between ICD rubrics 153 (colon + large bowel, unspecified) and 154 (rectum + rectosigmoid junction) is also subject to variability [20, 21]. When changes in the risk of cancers of the colon and rectum on migration appear to move in opposite directions, systematic differences in classification of colorectal cancers between these categories should be considered as a possible explanation. It is particularly obvious, for example, in studies of Polish migrants [22–24] suggesting a systematic bias towards recording rectal rather than colon cancer in Polish mortality data.

Mismatching numerator/denominator

Calculation of rates of incidence or mortality requires an estimate of person-years at risk, according to the variables under study. These normally are made from census data (or estimates based on these), typically broken down by rather few variables including, in addition to birthplace, age, sex and place of residence. It is obviously essential that migrant status is defined in an identical manner in the census and case/death data. However, even with the same definition, individuals may be classified in a different way in the two sources; Lilienfeld and associates [15] present unpublished data on differences between country-of-birth statements on death certificates and census returns for the U.S.A. in 1960 — this varied from a 10.8 per cent deficit on death certificates for U.K. birth to a 16.7 per cent excess for Ireland. A source of bias more difficult to detect results from migration which is related to the disease event itself—for example, when migrants return to their country of origin soon before death (so that mortality rates in the host country are underestimated).

A more practical difficulty in using population-at-risk data results from the fact that censuses are rather infrequent, and interpolations are needed to derive person-years at risk. This

can be quite prone to error when several variables are involved, and active migration is still occurring during the study period.

Selection bias

Migrant populations are a non-random (self-selected) sample of the population of their country of origin. Very often they come from quite limited geographical areas—migrants to the United States of Italian origin come mainly from the south of that country [25] and a large proportion of U.S. Chinese originate from Guangdong province [26], for example. Alternatively, the migrants may be special social or religious groups with quite distinctive cancer patterns—for example, Jews comprised a large proportion of the migrants from Central Europe in the late 1930s and 1940s. Migrants are often assumed to be healthier than the average population (the 'healthy migrant effect'); this may be because the fact of seeking a new life overseas implies a population that is resourceful and energetic (or at least not chronically ill), or because the sick and disabled are excluded by the immigration authorities of the host country. Conversely, it has been suggested [27] that permission for Jews to migrate to Israel from countries of the Soviet block was more easily obtained for those in ill health, giving rise to an 'unhealthy migrant effect'. The effect of selection bias is reduced if comparisons can be made between similar groups; this is usually impossible for the country of origin—migrant comparisons, although in the case of migrants from distinct geographical regions, it is obviously more appropriate to use the cancer rates from these for comparisons, rather than the national country of origin rates. It is possible to check for the 'healthy/unhealthy migrant effect' if risk according to duration of stay in the new country can be estimated a significant change in rates from those in the host country in recent migrants should suggest this form of bias. Swerdlow [28] found no sign of any such effect in Vietnamese refugees to England and Wales, and Steinitz and associates [27] found that exclusion of cancer cases diagnosed within a year of arrival in Israel made no difference to relative risks for short stay (less than 10 years) migrants.

Confounding

Several demographic variables recorded by cancer registries or on death certificates can be considered as confounders—related both to disease risk and exposure (migrant status)—in a study aiming to investigate the effect of birthplace on disease risk. These include date of diagnosis/death, marital status, place of residence, and possibly ethnic group, occupation, socio-economic status (such as employment status, income, educational level, etc).

Migrants are in the first place rarely distributed homogeneously in their new host country: they tend to settle in certain areas, generally in urban areas, and the establishment of a migrant 'colony' in a place tends to draw later migrants to settle there. The plethora of 'cancer atlases' testifies to the importance of geographical variation in cancer risk within countries, so it is inappropriate to compare disease rates in migrants with the entire population of the host country. Table 1 illustrates an example of confounding by place of residence. Polish migrants to Argentina live mainly in Buenos Aires (81.2%, compared with 48% of the local-born), where mortality rates from colon and breast cancer are higher than elsewhere. Adjustment for place of residence reduces the relative risk of both cancers, and for colon cancer the difference from the local-born is no longer statistically significant.

Social class and occupation are also known to be strong determinants of cancer risk, and it is often clear from census data that migrants are over-represented in specific occupational categories, and are atypical of the general population in their socio-economic profile. Meaningful comparisons should therefore take the social dimension into account.

Temporal trends in cancer incidence or mortality may also be different in the migrant population and in the host country. When data from 1 long time period are used, the relative risk between them may differ according to time period. This is particularly troublesome when the effect of duration of stay is being studied, since, in general, data from more recent time periods will contain more migrants with long periods of residence than those from earlier years: an adjustment for time period is thus necessary.

However, except for age-standardisation, few migrant studies make any attempt to control for the effect of potential confounders. Investigators may identify differences in socio-economic status or geographical location as the reasons for differences in disease rates between migrants and the local population (e.g [16, 29], but rarely attempt to control for such sources of variation. Probably, this is because of the difficulty in doing so with the traditional "descriptive" methods of data analysis—the calculation of age-standardised rates or ratios; standardisation for more than two or three variables is impracticable, and impossible if population-at-risk data for all variables of interest are unknown. However, since the main interest is less in the actual rates than the ratios between them (country of origin versus migrants versus host population), it

Table 1. Confounding by place of residence in a study of cancer mortality in Polish migrants to Argentina (data from [22, 70])

Cancer mortality and place of residence	Buenos Aires	Elsewhere in Argentina
Relative risk of colon cancer (M)	1.9	1.0
Relative risk of breast cancer (F)	1.4	1.0
Place of residence and birthplace	Buenos Aires	Elsewhere in Argentina
Born in Poland	81.2%	18.8%
Born in Argentina	47.9%	52.1%
Cancer mortality and birthplace (relative risk in Poland-born versus Argentina-born (1.0))		
	Crude	Adjusted for place of residence
Colon cancer (M)	1.34 (1.06–1.68)	1.16 (0.95–1.43)
Breast cancer (F)	0.90 (0.75–1.08)	0.82 (0.63–1.05)

may well be possible to estimate relative risks, while controlling for the effects of the suspect confounding variables. When these are few, stratified analyses and estimation of Mantel–Haenszel estimates are appropriate; in the presence of several potential confounders, it is necessary to use regression models—Poisson regression when population-at-risk is known, logistic regression of case–control data when it is not.

METHODS FOR MIGRANT STUDIES

A variety of analytical methods may be used; they have in common the exposure variable 'migrant status' for which cancer risk is estimated. It is very rarely feasible to carry out a true cohort study, which involves enrolling individuals at the time of their migration, and following the cohort for deaths, loss to follow-up, and disease events, with accurate estimation of the person-years at risk (e.g. [28]). More usually, age-standardised rates are calculated for migrants and natives of the host country, based upon estimates of the population at risk from census data. A number of studies show mortality or incidence rates for migrants, host country and country of origin, standardised to the world population, or to the host country population [10], or ratios of age-standardised rates, rather than the rates themselves [16, 30]. Indirect standardisation is often preferred to direct standardisation to increase statistical precision for rarer tumour sites and smaller migrant groups; it involves calculation of standardised mortality or incidence ratios, with the age-specific rates in the host country as the standard [31–33].

When the population-at-risk, cross-classified by the variables of interest, cannot be estimated, one has to rely entirely on the numerator data, that is, on proportionate incidence or mortality data. Indirect standardisation techniques have been applied in such instances, involving the calculation of proportionate mortality or incidence ratios, with the fraction of deaths or of cases due to specific causes in the host country as the standard [27, 34].

Recently, in order to control for confounding, standard applications of log-linear modelling have been used for investigating cancer risk among migrants [22, 27, 35–37]. When the population-at-risk in each cell of the cross-classification is available, it is assumed that the number of cases or deaths per cell has a Poisson distribution, with mean value proportional to the number of person-years at risk, and that the logarithm of the rate is a linear function of the classification variables. Poisson regression provides adjusted relative risk estimates for migrants versus host country.

When the person-years at risk for the variables of interest are unknown, relative risks are approximated by odds ratios from case–control comparisons. Controls may be selected specifically to represent the population at risk in a true case-control study (e.g. [2]). When only cancer registrations or mortality data are available comparison of migrant status is between cases of the cancer of interest, and cancers at other sites, or deaths from other causes. Unconditional logistic regression or stratified analyses are performed to obtain maximum likelihood estimates of the odds ratios [38]. The odds ratio is a much better estimator of relative risk than the proportional mortality (incidence) ratio [39], the use of which should be abandoned.

The statistical methods used in the studies of cancer risk in migrants have been reviewed [40]. The odds ratio values based on logistic regression are heavily dependent on the choice of the controls: if the risk for the causes used as controls is unrelated to migration, the estimates from the logistic model for the effects of migration closely approximate those which would be obtained using Poisson regression with denominator populations. When the population-at-risk is known, Poisson regression, standardised rate ratios and standardised mortality or incidence ratios provide estimates of cancer risk in migrants which are generally quite close. The advantages of statistical modelling over standardisation and related techniques are: (1) modelling facilitates the consideration of the simultaneous effects of several independent variables on risk; (2) the effect of quantitative variables such as duration of residence in host country can be modelled in terms of dose–response relationships, which makes more economical use of the data; and (3) relative risk estimates obtained by model fitting have greater numerical stability than those computed from standardised rates [41].

EXAMPLES OF MIGRANT STUDIES

Single-comparison studies

These are the least informative, showing differences in risk between migrants and the locally born, but providing no information on the populations from which the migrants came. Absence of data relating to the country of origin may result from the non-existence of appropriate sources (for example, no cancer registry may be present from which incidence rates can be found), or that data are unavailable for the appropriate population subgroups from which the migrants came.

Figure 1 shows the relative risks (standardised rate ratios) for cancer of the breast in Jewish migrants to Israel [27]. There is a more than 5-fold range in risk, presumably related to some important differences in lifestyle; unfortunately, there is no information available on the incidence of breast cancer in the Jewish populations of the countries of origin.

Two-comparison studies

These are the most common type of study reported. The results are interpreted in terms of the degree to which the risk for different cancer sites changes in the migrant population away from that in the country of origin and towards that of natives in the new host country. Examples are the several studies which examine mortality rates in populations of predominantly European origin moving to the United States [14, 15, 42], Australia [43, 44], England & Wales [34, 45] and South America [22, 37]. The fact that the data for the two comparisons came from different sources must always be borne in mind, and bias in the first (country of origin) probably explains some of the findings in published studies.

Figure 2 shows results from a collaborative study of cancer risks in Italian migrant populations [46]. The risk of mortality from cancer of the pancreas in men is plotted for Italian migrants and the country of origin (Italy) with reference to that in the host countries (1.0). An attempt is made to allow for the selection bias which results from migrants to several of the host countries coming mainly from southern Italy, by presenting relative risks for both the south of Italy and the whole country. The relative risks for the migrants have been adjusted for the available confounding variables (mainly time period and region of residence) in addition to age. The risks in migrants show quite marked changes towards those in the new host country (where, in general, risks are higher than in Italy, and particularly than in the south of Italy). For migrants to France, the results demonstrate the phenomenon of 'over-

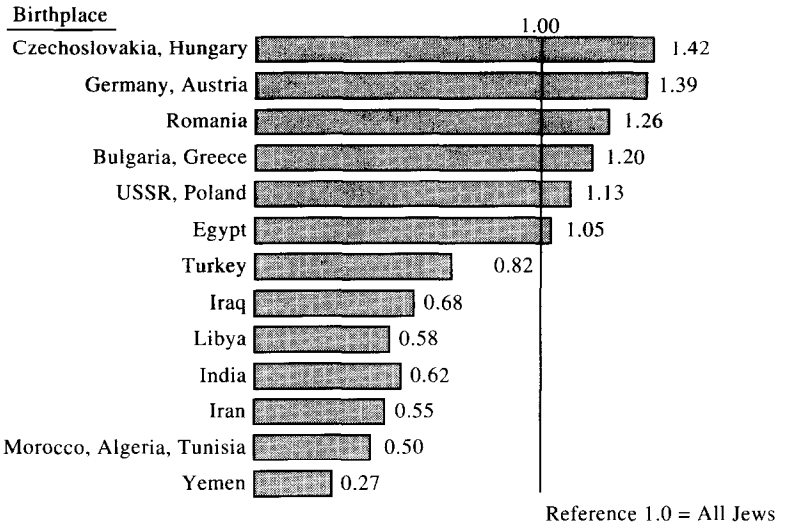

Figure 1. Relative risk (standardised incidence ratio) of breast cancer in Israel (1961–1981) by birthplace. Reference category = all Jews.

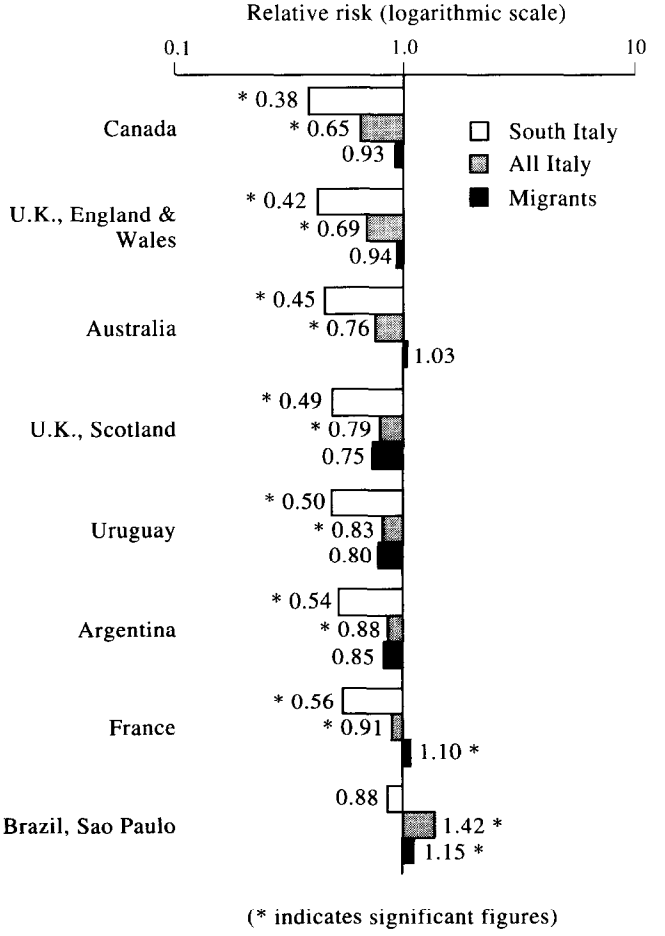

Figure 2. Relative risk of pancreatic cancer mortality in males in Italy (national, south) and migrants from Italy relative to eight host country populations (risk = 1.0).

shoot', described above. Pancreas cancer is an excessively popular diagnosis on death certificates in France (as shown by the ratio of deaths to incident cases, 1.67:1, in French cancer registries [19]). It is quite likely that mortality rates in France are actually inferior to those in Italy (as are incidence rates), and that the migrant rates slightly above the local-born are entirely consistent with a convergence of risk.

Studies with a time dimension

Studies of the effect of duration of residence or age at migration. Relatively few published studies have been able to study cancer rates in first-generation migrants by duration of stay (or age at arrival) in the host country.

Data from the Los Angeles County cancer registry have been used to separate migrants in Los Angeles into those who arrived in the U.S.A. in childhood, and those who came as adults [47–49]. The method used was to calculate age at issue of social security number; if the age at issuance was over the 90th percentile of that for the same birth cohort born in the U.S.A., it was assumed that the individual had entered the workforce late, and hence probably migrated in adulthood.

The routine recording in Australian death certificates of date of migration has permitted several studies of mortality in relation to duration of residence in Australia; the findings in relation to gastro-intestinal cancers [16, 50] and to malignant melanoma [51] are of particular interest.

Figure 3 [1] shows the risk of death from melanoma of six migrant populations in relation to either duration of stay or age at arrival, using the Australia-born as the reference group. Since these two variables are completely interdependent (long durations of stay are associated with early ages at arrival), it is impossible to separate their effects. The figure gives the impression that arrival in childhood is associated with relatively high risks, but that in age groups 15–24 years, and 25 years and above, risk remains significantly lower than that of the Australia-born. The irregular increase in risk with duration of stay, with a relatively sharp increase after 30 years for many of the groups makes little biological sense, and could well reflect the excess of childhood immigrants in the long stay category.

The Israel Cancer Registry records date of migration for all cases of cancer. This has allowed the risk of cancer to be examined for different populations of migrants in relation to their duration of residence in Israel [27, 35]. Figure 4 illustrates the risk of cervical cancer in migrants to Israel, relative to the local-born, in relation to duration of stay. The data derive from a long time period (1961–1981) during which there were marked temporal trends in the risk of cervical cancer, and in particular a striking increase in incidence (× 2.5) in the Israel-born, but little change or even slight declines in risk for the migrant groups. Because most migration took place before the data collection period, duration of stay is strongly confounded by time period (short duration-of-stay cases come mainly from earlier periods, and vice versa), and adjustment for time period has a very striking effect on relative risks (Figure 4). These observations may be explicable in terms of cumulative exposure to Pap smear testing following migration, since the high risk of cervical cancer in these populations is well known to clinicians [27, 35].

Studies of second and subsequent generations of migrants. The best known studies are those of Japanese in the U.S.A [48, 49, 52–55] and Hawaii [10, 56], and of Chinese in the U.S.A [26, 57], distinguishing the foreign-born (first-generation migrants) from the U.S.A.-born (their offspring). The results of these studies (up to 1987) have been reviewed by Thomas and Karagas [58]. Figure 5 [6] shows incidence rates of stom-

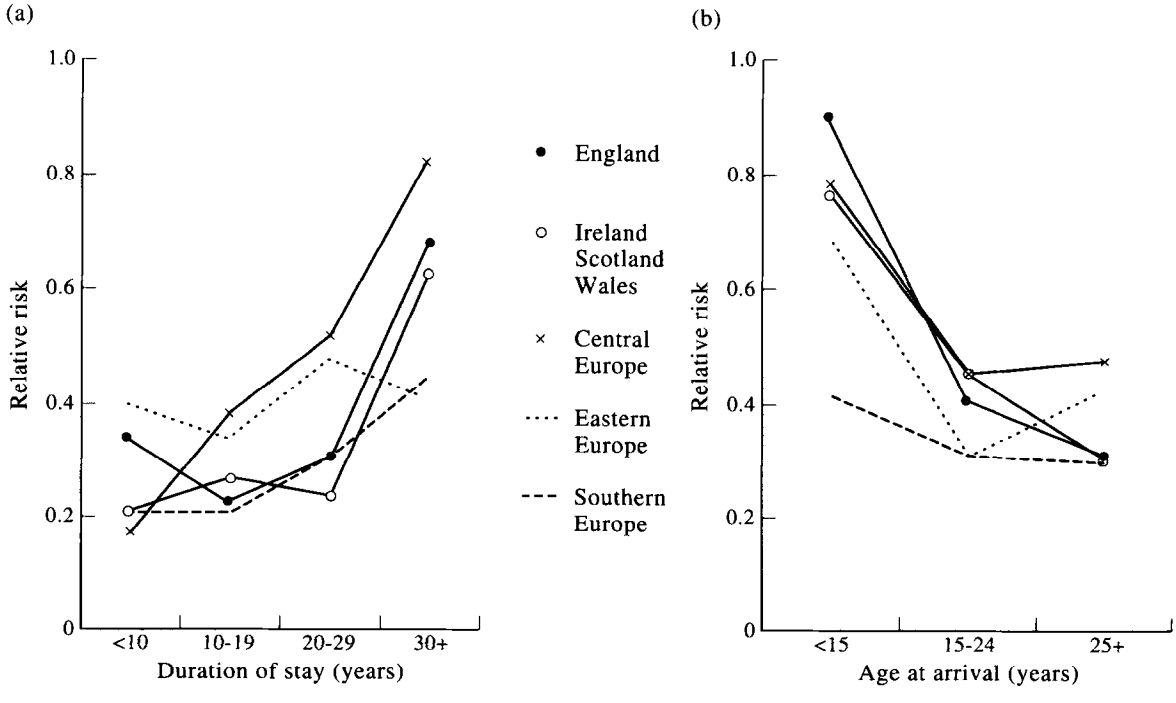

Figure 3. Melanoma in male migrants to Australia. Risks relative to Australia-born by duration of stay in Australia (a) and age at arrival (b).

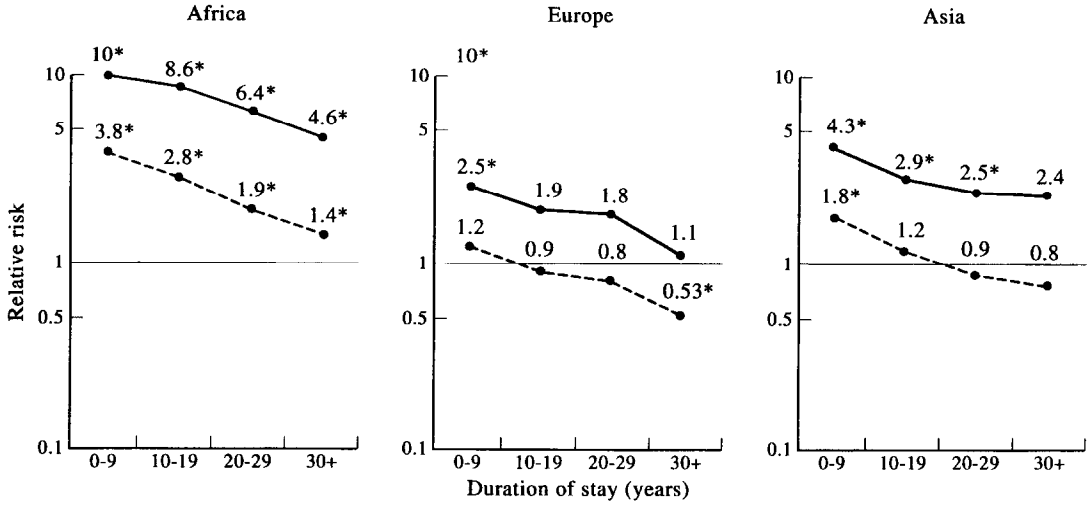

Figure 4. Risk of cervical cancer in migrants to Israel (1961–1981), by birthplace and duration of stay with (——) and without (– – –) adjustment for time period. Reference category = born in Israel [36]. Values which are significantly different from 1.0 ($P < 0.05$) are marked with an asterisk.

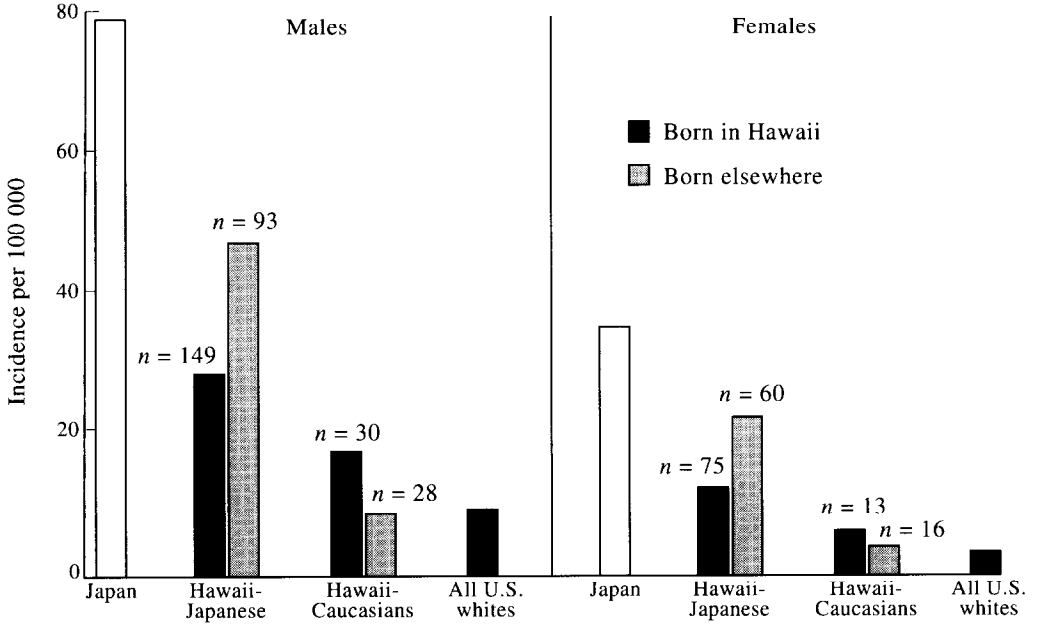

Figure 5. Age-adjusted stomach cancer incidence in Hawaii Japanese and Caucasians by place of birth, 1973–1977. Sources: Hawaiians, Kolonel and colleagues [11]; U.S. whites (1973–1977), Young and colleagues [68]; Japan (1975), Hanai and colleagues [69].

ach cancer in two ethnic groups in Hawaii—Japanese and Caucasian (white)—in relation to place of birth, and provides rates for the populations of the countries of origin—Japan and U.S.A. Incidence rates in Japanese migrants to Hawaii are lower than in Japan, and in Hawaii-born Japanese they are lower still, but still higher than in the white population. conversely, in the white population of Hawaii, there is an increase in stomach cancer risk in the locally born compared to U.S. whites (or migrants from the U.S.A).

The Singapore Cancer Registry records both place of birth and dialect group, and can thus calculate incidence in Chinese migrants and their offspring [59].

Birthplace of parents, which is sometimes recorded on death certificates or cancer registries, has been little used to study cancer risk in offspring of migrants. Balzi and associates [60] used mortality data from Canada to study cancer risks in Italian migrants and Canadian-born individuals of Italian parentage. The latter group was separated into either those with two parents born in Italy, or only one. Figure 6 shows results for the two most common cancers, stomach and lung. The risk of stomach cancer, which in migrants is 2–3 times that in the reference population (Canada-born of Canadian parents), is no longer significantly raised in their offspring, while trends in the opposite direction are seen for lung cancer. Steinitz and colleagues [61], using data from the Israel Cancer Registry, present SMRs (standard morbidity ratios) for nasopharynx cancer and Ewing's sarcoma for the Israel-born population according to parents' birthplace. Individuals with par-

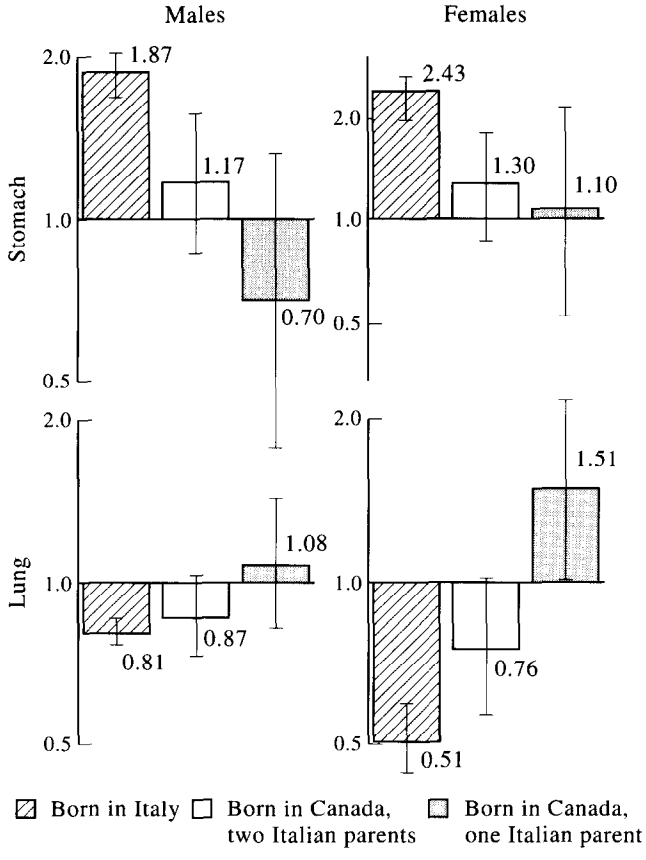

Figure 6. Odds ratios (with 95% confidence intervals) for Italian migrants and their offspring, relative to Canada-born individuals with two Canada-born parents (1.0). ORs adjusted for age, province of residence and time period [60].

ents from North Africa retained the increased risk of nasopharynx cancer seen in migrants from that area.

Studies which combine temporal information and ancestry of migrants. In the study by Ziegler and colleagues [2] of breast cancer in Asian women in the United States, personal interviews of cases and controls allowed collection of extensive information on migration history and ancestry. It was thus possible to look not only at duration of stay (or age at arrival) as a determinant of risk, but also at the effect of birthplace of parents and grandparents. Migrants who had lived in the West for a decade or longer had a risk 80% higher than more recent arrivals. Asian Americans born in the West had incidence rates 60% higher than in migrants (similar to rates in U.S. whites), and among this group risk was determined by whether their grandparents, and especially grandmothers, were born in the East or West.

Studies which include information on exposures

In this type of study, population-level data are available for the migrants and the population of the host country, and sometimes for country or origin also, on the prevalence of exposure to possible aetiological factors. A rather simple ecological-level comparison is therefore possible. Two groups of studies have reported on consumption of dietary items and alcohol.

McMichael and colleagues [16] related mortality rates from gastro-intestinal cancers in European migrants to Australia with per capita food consumption data from a period 10 years earlier in Australia and the countries of origin; results from a national dietary survey were included later [31].

For the Japanese population of Hawaii, the dietary intake of a range of nutrients can be estimated from the control subjects in case–control studies [11] and from special surveys [10, 12], and the Japanese population (as well as Hawaii whites) can be separated into those born in Hawaii or elsewhere. The Japan–Hawaii heart study also provides a large amount of information on dietary patterns in Japan and Hawaii [62, 63].

The use of such exposure information in the interpretation of changes in risk of cancer in migrant populations can be seen by comparing the rates for stomach cancer in Japan (Figure 5) with the dietary data in Table 2. Thus, second-generation Japanese eat less pickled vegetables and dried salted fish than Japanese migrants (born in Japan), whereas the whites who were born in Hawaii seem to eat these foods more frequently than whites born elsewhere. Both of these items have been associated with an increase in the risk of stomach cancer in case–control studies [64, 65]. The observations were similar for consumption of rice (and total carbohydrate intake), also suggested as aetiologically important in some studies [66, 67].

CONCLUSIONS

Migrant studies have moved on from relatively simple comparisons of incidence and mortality rates to utilise a much

*Table 2. Mean dietary intakes in relation to stomach cancer incidence by race, sex and place of birth**

	Born in Hawaii	Stomach cancer incidence†	Dried salt fish	Pickled vegetables	Rice
Japanese male	Yes	112	0.1	2.8	7.4
	No	156	0.2	3.1	8.7
Japanese female	Yes	48	0.1	2.8	7.2
	No	54	0.3	4.1	7.5
Caucasian male	Yes	61	0.1	0.4	5.3
	No	31	0.0	0.3	2.3
Caucasian female	Yes	23	0.0	0.3	4.3
	No	16	0.0	0.1	1.8

*Intakes expressed as average number of times consumed per week (data taken from [11]).
†Age-standardised rate per 100 000 adjusted to world population aged 45 years and over.

wider range of appropriate epidemiological methods. Interpreted with care, bearing in mind the potential sources of bias, they can provide considerable information on change in cancer risk in response to changes in external environment and/or lifestyle. It is not the fact that rates in migrants converge on those of their host country which is of interest—it would be surprising indeed if it were otherwise—rather, it is the extent and rate of change that are informative. It follows that studies which can provide estimates of risk relative to age at migration, duration of stay, and between generations, will be the most useful. Thus, the importance of genetic susceptibility in determining risk is suggested by the persistence of characteristic rates between generations, as observed with nasopharynx cancer, malignant melanoma, and possibly testis cancer. Conversely, a rapid change in risk following migration implies that lifestyle/environment are important in aetiology, and that the relevant agents act late in carcinogenesis (e.g. large bowel cancer, cervix cancer). For other cancers, change following migration is slower, although evident in the comparisons between migrants and their offspring; this pattern suggests that exposures early in life are the most relevant (stomach cancer, breast cancer, thyroid cancer). Because the information on individual subjects is limited, we cannot be sure which components of change in lifestyle/environment are important; there may be clues when population-level exposure data are available, but the inferences to be drawn necessarily remain those of ecological, between population, comparisons. Nevertheless, migrant studies provide useful data in another context—predicting the extent of the change which might reasonably be expected from community-level prevention programmes, particularly in the realm of dietary change.

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