Letters to the Editor

Correspondence re: Risch, N.: Genetic Epidemiology of Cancer: Interpreting Family and Twin Studies and Their Implications for Molecular Genetic Approaches. Cancer Epidemiol. Biomark. Prev., *10:* 733–741, 2001.

Letter

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Dr. Risch published a challenging review on genetic epidemiology of cancer last year (1). Dr. Risch based his major argument favoring dominant or additive models, and disfavoring polygenic threshold models, on the analysis of our Nordic twin data (2). According to his Table 3, if the risk ratio for cancer between monozygotic and dizygotic twins (R_{MD}) was 2, the effect was attributed to a dominant gene or additive effects; if it was >2, it was recessive or polygenic (nonadditive); if it was <2, it was environmental. However, $R_{MD} = 2$ also when equally common polygenic ($R_{MD} = 3$, *e.g.*, prostate cancer) and environmental ($R_{MD} = 1$, *e.g.*, lung cancer) cancers are combined, similar to summation of all cancers by Dr. Risch. In fact, only breast cancer gave a value close to 2, but even this may be a sum effect of polygenic and environmental components. This kind of analysis can provide a case for recessive and nonadditive polygenic effects (when $R_{MD} \gg 2$) or environmental effects (when $R_{MD} \ll 2$), but it proves nothing for heterogeneous cancers at $R_{MD} \sim 2$. Dr. Risch's conclusion, "Thus, the observed value of R_{MD} conforms poorly to the predictions of the multifactorial threshold model but extremely well to the single-locus or additive genetic model . . ." is flawed, because heterogeneous etiologies or cancers cannot be averaged.

Dr. Risch's general tone was that we underestimated the heritable effects in cancers in our twin study, even though for colorectal, breast, and prostate cancers, they explained 35, 27, and 42% of the variation, respectively (2). Dr. Risch invoked "empirical data" to support his case but showed none in his paper. I will give PAFs[1] for familial cancers in 0–61-year-old offspring from a similar cancer in parents by calculating these from published familial risks (3). This is in keeping with Dr. Risch's "single-locus or additive genetic models" over "multifactorial threshold models," used in the twin study. The PAF values for cancers in this midlife population ranged from 0.3% for testis cancer to 4.9% for colorectum (Table 1). Prostate with a PAF of 10.8% was an exception, but the age of onset considered, 0–61 years, was very young for prostate cancer, biasing the result heavily toward hereditary cases. Thus, the "empirical data" failed to make a case for overwhelming heritable effects. Table 1 also shows that Dr. Risch's selection of PAF values for familial effect, that ranged from 7.7 to 82.1% in his Table 5, was entirely unrealistic.

Table 1 SIRs,[a] familial proportions (% of all affected offspring with an affected parent), and PAFs for parent-offspring familial relationships among 0–61-year-old offspring, based on the Swedish Family-Cancer Database, modified from Ref. 3.

Site	SIR	Proportion (%)	Familial PAF (%)
Stomach	1.7	4.5	1.9
Colorectum	2.0	9.8	4.9
Lung	1.6	5.6	2.1
Breast, female	1.9	8.1	3.8
Cervix	1.9	4.0	1.9
Endometrium	2.9	3.1	2.0
Ovary	2.8	3.1	2.0
Prostate	2.7	17.2	10.8
Testis	4.3	0.4	0.3
Kidney	1.5	2.9	1.4
Bladder	1.5	3.4	1.7
Melanoma	2.4	2.3	1.3
Skin, squamous	2.2	3.4	1.9
Nervous system	1.7	2.5	1.0
Thyroid	6.9	2.5	2.1
Other endocrine	2.5	2.1	1.4
Lymphoma	1.6	1.0	0.4
Leukemia	1.8	2.4	1.1

[a] SIR, standardized incidence ratios.

In conclusion, empirical PAF values for familial cancer were far lower than the heritable effects of common cancers predicted by the Nordic twin study, which may show our limited understanding of carcinogenic mechanisms (4, 5). In spite of these uncertainties, the cancer preventive perspectives of identified, even rare heritable cancers, and their potential implications for somatic cancers and carcinogenic mechanisms, should be gratifying enough to keep us working.

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[1] The abbreviation used is: PAF, population-attributable fraction.

Reply

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Dr. Hemminki raises several interesting points that require additional clarification and discussion. These issues generally relate to: (*a*) evidence of genetic *versus* environmental causes of familial aggregation; (*b*) mode of inheritance (including number and interaction effects of contributing alleles and loci); and (*c*) measures of genetic contribution to a disease (*i.e.* cancer).

Evidence of Genetic Heritability. In their Nordic twin analysis, Lichtenstein *et al.* (1) conclude: "Inherited genetic factors make a minor contribution to susceptibility to most types of neoplasms. This finding indicates that the environment has the principal role in causing sporadic cancer." Dr. Hemminki appears to reaffirm this conclusion, although he notes that a few cancers (colorectal, breast, and prostate) had significant heritability estimates in their analysis. These three cancers are among the most frequent, leading to the statistical significance of their heritability estimates. What I demonstrated in the reanalysis of the Nordic twin data, as well as the analysis of the Utah and Swedish family study data, is that most, if not all cancers (including the rare ones) were consistent with a similar degree of familial aggregation and twin concordance. The rarer cancers appeared to be less heritable only because of small numbers (2, 3). Dr. Hemminki also notes that familial aggregation may be attributable to environmental factors as well as genetic ones. To this end, we can compare the recurrence risk of various same-site cancers among the first-degree relatives from the Utah study (4), the offspring and siblings in the Swedish family study (5, 6), and the spouses of cancer index cases from the same Swedish study (6). Results are in Table 1. I have calculated the FRR[1] for each type of relative, similar to the original studies and my previous analysis (2). Table 1 gives a remarkably consistent picture of the role of genetics *versus* environment in the familial aggregation of most cancers. The median and range for FRR for all of the first-degree relatives in Utah is 2.2 (range, 1.3–8.6), similar to the values for offspring in Sweden, 2.1 (range, 1.9–15.6). For spouses, the comparable numbers are 1.1 (range, 0.4–1.4). The Swedish siblings and early onset groups are discussed additionally below. The low spouse FRR led Hemminki *et al.* (6) to conclude "familial cancer risks between parents and offspring are likely to be more due to heritable rather than environmental effects." That being the case, the consistently elevated FRR (2.1) for first-degree relatives across cancer sites argues for a genetic interpretation of that number. Furthermore, I have plotted the FRR for the same 16 cancer sites for Utah and Sweden (Fig. 1). Interestingly, there are 3 sites with significantly elevated FRRs in both studies (thyroid, testis, and multiple myeloma). However, after removing those 3 sites, there is no residual correlation in FRRs for the remaining 13 sites between studies. Thus, the variation around the FRR value of 2.0 for the residual sites in each study is likely attributable mostly to statistical noise. A similar conclusion holds for the twin concordances, where the recurrence risk ratios for monozygotic twins (λ_M) and dizygotic twins (λ_D) are consistent across cancer sites (values of 7.6 and 4.0, respectively) except for breast (values of 4.1 and 2.5, respectively).

Mode of Inheritance. Differentiating between various modes of inheritance, even major gene *versus* polygenic, can be a difficult task with family data alone and without identified genes. Sometimes, segregation analysis can be revealing as has been the case for breast, ovarian, and colon cancers. As I indicated previously, the twin concordance ratio $R_{MD} = (\lambda_M - 1)/(\lambda_D - 1)$ can also be indicative. A value of 2 is consistent with additive or dominant gene effects, while $R_{MD} > 2$ is consistent with gene interactions or polygenic inheritance. Because the recurrence data from spouses suggests minimal effects of shared environment (6) (with the possible exception of lung cancer, for which smoking is a major confounder), the consistent value of $R_{MD} = 2$ across cancer sites argues against strong allelic or gene interactions. Although the R_{MD} values for individual cancer sites deviate from the average value of 2, I showed previously that this deviation was entirely explainable by sample size and statistical fluctuation (Table 4 in Ref. 2). By contrast, other common diseases with more complex patterns of inheritance consistent with polygenic inheritance or gene interactions show dramatically higher values of R_{MD} (Table 2).

Recessive inheritance can be revealed by elevated risks to siblings *versus* offspring or parents of index cases. As I discussed previously, for cancer these comparisons are often confounded by age of onset. Table 1 reveals that the Swedish data strongly support dominant or additive inheritance with an age of onset effect rather than recessive inheritance. While for all of the index cases the median FRR for offspring is 2.1, it rises to 4.2 for offspring of index cases with onset before age 50. These numbers are virtually identical to those from Utah. In the sibling study, the average age of onset of the index cases was 38–42 years of age (5), comparable to index cases in the early onset subgroup used for offspring risks. The observed median sibling FRR of 3.5 is, thus, comparable to the offspring FRR for a similarly aged group of index subjects. It is also noteworthy that the age of onset effect is not observed in spouses, supporting its origin being genetic.

Dr. Hemminki also comments on risks to offspring of dual matings as discriminative of mode of inheritance. Unfortunately, the numbers reported (7) are so small ($n = 5$ for breast cancer and $n = 2$ for melanoma) and confidence intervals so large that little can be said on this point with confidence. He also comments on the strong evidence of association of family history with risk of multiple primary tumors found in his studies (8, 9) as has also been observed by others (10). Indeed, these elevated risks are most consistent with major dominant gene effects (10, 11). The fact that increased risk of subsequent primary tumors in first diagnosed cases was also observed in the absence of a family history was taken as evidence of polygenic inheritance (8); however, no argument as to why such an effect should be polygenic has been given.

Measures of Genetic Contribution. Dr. Hemminki has calculated the PAF associated with a positive family history. What I calculated (Table 5 of Ref. 2) is the PAF associated with specific gene effects. The two are not the same. What I showed

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[1] The abbreviations used are: FRR, family risk ratio; PAF, population attributable fraction.

Table 1 FRRs in Utah and Sweden

	Utah			Sweden						
	All first degree			Offspring			Siblings	Spouses		
	All	Early onset	Ratio[a]	All	Onset <50	Ratio		All	Onset <50	Ratio
Number of sites	26	9	9	17	16	16	17	17	17	17
Median FRR	2.2	4.1	1.9	1.9	4.2	2.2	3.5	1.1	1.0	1.0
Range	1.3–8.6	1.8–9.0	1.0–4.5	1.5–9.5	1.9–15.6	1.0–3.9	2.0–12.4	0.4–1.4	0.0–2.9	0.0–2.5

[a] Ratio is the ratio of FRRs for early onset *versus* all index cases. In Utah, early onset is defined as before age 50 or age 60, depending on site.

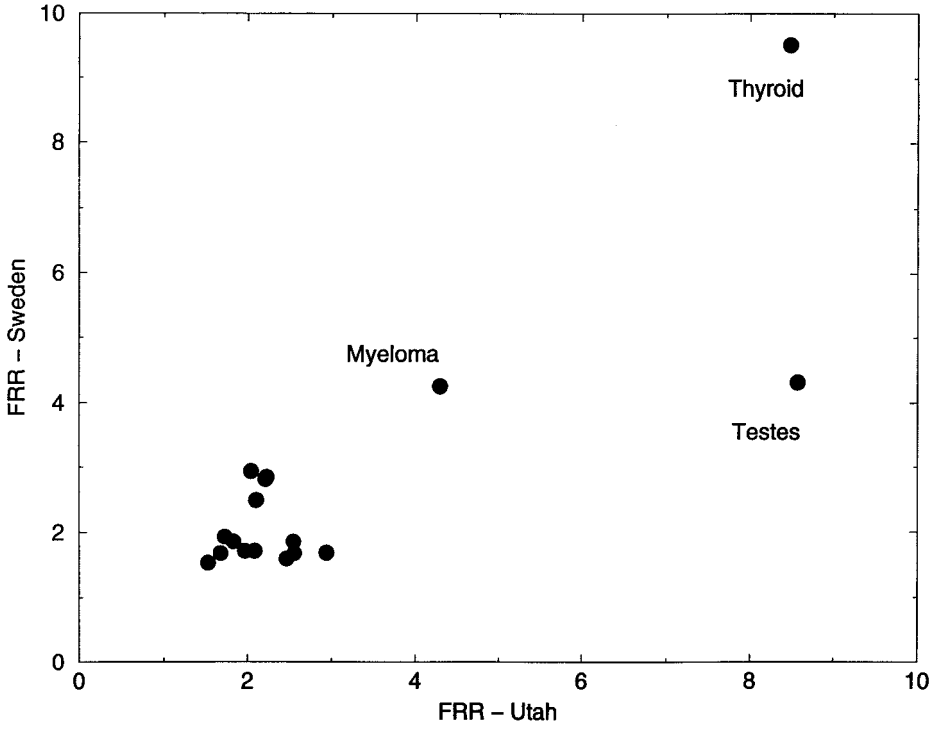

Fig. 1. FRR for Utah first-degree relatives (4) versus Swedish offspring (5).

Table 2 Twin relative risks and R_{MD} for other diseases

Disease	Prevalence	λ_M	λ_D	R_{MD}
Type 1 diabetes	0.4%	95	20	4.9
Schizophrenia	1.0%	48	10	5.2
Multiple sclerosis	0.1%	270	34	8.2
Crohn's disease	0.1%	425	40	10.9
Autism	0.1%	750	30	25.8

is that a specific gene or genes could produce the identical family recurrence patterns and heritability estimates, yet dramatically different PAFs depending on their allele frequencies and relative risks. Consider the following notation: K_p = prevalence in parents; K_o = prevalence in offspring; R_a = risk to offspring of affected parent; R_u = risk to offspring of unaffected parent; $RR_{au} = R_a/R_u$. Then the family history PAF can be approximated by $2K_p (RR_{au} - 1)$ when both sexes are affected or half that value for cancers affecting one sex only. As can be seen from this formula, the family history PAF depends on the prevalence of the tumor. This is consistent with the results given by Hemminki (his Table 1) which show the highest PAFs for the most common cancers (breast, prostate, and colorectum). Furthermore, for the examples I gave in Table 5 of (2), the family history PAF would be ~5% for breast cancer, and ranging between 0.5% and 1.5% for other tumors with frequencies (K_p) ranging from 0.1% to 1%, similar to the numbers given by Dr. Hemminki. However, the same table showed that these numbers are consistent with individual genes contributing small or very large PAFs.

I agree that the cancer susceptibility genes identified to date (*BRCA1*, *BRCA2*, and *HNPCC*) account for only a small PAF for breast and colon cancers, although a larger proportion (12–27%) of ovarian cancer (12, 13). However, it is also clear that these genes do not explain the full familial aggregation of these tumors, supporting the existence of additional loci for these and other cancers. These additional loci may individually or collectively contribute substantial PAFs.

Finally, none of these comments should be taken to detract from the value of the impressive family and twin-based cohorts that Dr. Hemminki has developed and described. These remarkable data should be the subject of considerable additional discussion, analysis, and interpretation.

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