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Screening-related prevalence and incidence for non-recurrent diseases

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ABSTRACT: Expressions for prevalence (P) and incidence (I) in open dynamic populations are derived. When screenings are performed every s:th year, P and I will be functions of s. It is shown how the true values of P and I, which would have been obtained with continuous screening, can be estimated from screening data. A solution is also given to the following problem: Given that subsets of the population have different P's and I's and that resources are limited so only a fraction of the total population can be screened every year, which should be screened and how often in order to maximize the total proportion of detected cases?

KEY WORDS: Epidemiology, open dynamic population, prevalence, incidence, screening, optimality.

1. Introduction

The epidemiological characterization of a disease in a population is often expressed in terms of *prevalence* (P) and *incidence* (I). In an open dynamic population, P refers to the proportion of diseased individuals at a given point in time whereas I refers to the rate of new ocurrences of the disease. These concepts, which reflect the collective actual health state in a population, should not be confused with individual risk measures like probability and hazard of developing the disease, as will be made clear below.

Periodic health controls or *screenings* can be effective for early detection of diseases, and data from screenings can be used to estimate P and I. This will be of special importance in countries where routines for collecting medical data is less developed, or for diseases which rarely can be detected by the patients, such as diabetic retinopathy (cf. [SUS 82]). Here, an unknown number of never detected cases is to be expected if not screenings are performed.

In this paper expressions for P and I will be presented for non-recurrent diseases, which allows an arbitrary proportion of the population to be recovered from the disease. Similar expressions have been derived earlier under the assumptions that there is no recovery from the disease and that the disease shortens the remaining life time of the individual [ALH 92]. This may be true for some diseases, but it is not generally true for breast cancer, thigh-bone fractures, venereal diseases or schizophrenia, to mention a few examples. For diseases which can only be detected at screenings performed every s:th year, P and I will be functions of s, P(s) and I(s). These screening-related measures tend to zero as s→∞ and to P and I, the values which would have been obtained with continuous screening, as s→0. The differences between P and P(s) and between I and I(s) can be used to judge the benefit of a screening program beynd other measures such as lead time, i e. the time by which the diagnosis is advanced by screening [ZEL 69]. The screening-related measures can also be used to find an optimal solution of the following problem: Given that subsets of the population have different P's and I's and that resources are limited so only a fraction of the population can be screened every year, which shall be screened and how often? These results will be applied, using data from a screening study for diabetic retinopathy in Sweden.

2. Notations and assumptions

In an open dynamic population P and I is composed of four components: (1) λ, the intensity by which the individuals enter the population, (2) the distribution of T, the period each individual spend in the population, (3) the distribution of Z, the time from the entrance into the population until the onset of the disease and (4) the distribution of R, the duration of the disease. λ and T is typically interpreted as birth rate and life time, respectively, but other interpretations are possible. For diseases which are exclusively subjected to patients with diabetes, λ is the rate of new cases of diabetes and T is the duration of the diabetes.

The following assumptions are made about the components:(1) λ is the constant intensity of a stationary Poisson process. This assumption will make P and I independent of λ. (2) T is a random variable with a continuous cumulative distribution function (cdf) $F_T(x)$ and survival function (sf)

$S_T(x)=1-F_T(x)$. (3) Z has the cdf $F_Z(x)=1-S_Z(x)$ which may have discrete steps and $F_Z(\infty)<1$ is the proportion of the population which eventually is diseased. (4) The duration R is allowed to depend on Z with conditional sf $S_R(x|z)=P(R>x|Z=z)$. A well-known example of the latter dependency is recovery from thigh-bone fracture which tends to take a longer time for elderly patients. Diseases which may cause, or at least are associated with factors which may cause the individuals death, will for convenience be called *mortal*. Diseases without the latter property are called *non-mortal*. The distinction will be of importance for P but not for I. The actual time each individual spend in the population is thus min(T, $Z+R$) for mortal diseases and T for non-mortal diseases. In the latter case R can be interpreted "as time to recovery" and when no recovery is possible $S_R(x|z)=1$ for all x,z. T is assumed to be independent of the pair (R,Z).

The following random functions will be used to describe the state of the population: For individuals entering the population in the time interval (t-y,t), L(t-y,t,x), LH(t-y,t,x) and LD(t-y,t,x) denote the number of individuals, healthy individuals and diseased individuals, respectively, at exact time t+x. The cumulative number of diseased individuals in (t,t+x) is denoted N(t-y,t,*x*) if the individuals entered the population in (t-y,t) and N(t,t+x,*x*) if the individuals entered the population in (t,t+x). Realizations of the first three functions can jump one step up or down, while realizations of the last two functions are non-decreasing and can only have jumps one step up. When x=0 and y→∞ it is shown in the Appendix at the end of the paper that L(t-y,t,x)→L, LH(t-y,t,x)→LH and LD(t-y,t,x)→LD in distribution where the indices of L, LH and LD have been dropped because the distributions of the latter are stationary. Similarly, as y→∞ N(t-y,t,*x*)+N(t,t+x,x)→N(*x*) in distribution, where the latter is stationary and only depends on x, the length of the interval. Thus, the following stationary random functions will be used:

L = Number of individuals
LH= Number of healthy individuals   [1]
LD= Number of diseased individuals
N(x)= Cumulated number of diseased individuals during x time units

For a non-recurrent disease it is natural to make the general definitions P='Size of the diseased population/Size of the population' and I='Number of occurrences per unit time during a period/Size of the population at the beginning of the period'. In terms of expected values of the functions in [1], P and I may be formally defined as

$$P=\frac{E(LD)}{E(L)} \quad , I=\frac{E(N(x))/x}{E(LH)} \tag{2}$$

A somewhat different definition of I is obtained if the denominator in [2] is replaced by E(L) (cf. [ELA 80], pp.32-35). This is less adequate when I is

intended to be a measure of the rate of new occurrences. It is also evident that E(LH) shall not include recovered individuals for non-mortal diseases.

3. Some general expressions for prevalence and incidence

The following expressions can be derived for the expectations of the random functions in [1] (cf. the Appendix at the end of the paper):

$$E(L) = \begin{cases} \lambda \int_0^\infty S_T(u)\left(S_Z(u) + \int_0^u S_R(u-z|z)dF_Z(z) \right)du & \text{(mortal diseases)} \\ \lambda \int_0^\infty S_T(u)du = \lambda \cdot E(T) & \text{(non-mortal diseases)} \end{cases} \quad [3a]$$

$$E(LH) = \lambda \int_0^\infty S_T(u)S_Z(u)du \qquad [3b]$$

$$E(LD) = \lambda \int_0^\infty S_T(u)\int_0^u S_R(u-z|z)dF_Z(z)du \qquad [3c]$$

$$E(N(x)) = \lambda \int_0^\infty S_T(u)dF_Z(u)\cdot x \qquad [3d]$$

In [3b], E(LH) remains the same for mortal and non-mortal diseases (recovered individuals are not included in E(LH)). This also holds for E(LD). When the density function $f_Z(x)$ exists, $dF_Z(x)$ is replaced by $f_Z(z)dz$.

The expressions in [3] inserted into [2] give P and I. The calculation of these quantities requires knowledge about the sf $S_T(x)$ which may not be feasible. It is often easier to get information about the times spent in the population from a cross sectional sample. These are realizations of the backward recurrence time, say V, with density $f_V(x)=S_T(x)/E(T)$ ([COX 65], p. 356). In terms of the latter, P for a non-mortal disease can be expressed in the following way:

$$P_{nm} = \int_0^\infty f_V(u)\int_0^u S_R(u-z|z)dF_Z(z)du \qquad [4]$$

When the disease is mortal for a proportion p_M of the population, P for the total population becomes

$$P_{tot} = \frac{P_{nm}}{\left(\int_0^\infty f_V(u)S_Z(u)du + P_{nm} \right) p_M + 1 - p_M} \qquad [5]$$

For both mortal and non-mortal diseases

$$I = \frac{\int_0^\infty f_V(u)dF_Z(u)}{\int_0^\infty f_V(u)S_Z(u)du} \qquad [6]$$

3.1. Cohort-specific P and I, probability and hazard

P and I are sometimes used synonymously with cumulative probability and hazard, respectively. To show the relations between the latter cocepts and P and I in open dynamic populations, consider a cohort of individuals entering the population in the time interval (t-y,t). The *cohort-specific P(x) and I(x)*, expressed as functions of x= time spent in the population, are

$$P(x) = \frac{E(LD(t-y,t,t+x))}{E(L(t-y,t,t+x))} \quad \text{and}$$

$$I(x) = \lim_{h \to 0} \frac{\left[E(N(t-y,t,x+h)) - E(N(t-y,t,x)) \right]/h}{E(LH(t-y,t,t+x))}$$

where all expectations are obtained from the expressions in the Appendix. By letting $y \to 0$ it is seen that

$$P(x) \to \begin{cases} \dfrac{\int_0^x S_R(x-z|z)dF_z(z)}{S_z(x) + \int_0^x S_R(x-z|z)dF_z(z)} & \text{(mortal diseases)} \\[4ex] \int_0^x S_R(x-z|z)dF_z(z) & \text{(non-mortal diseases)} \end{cases}$$

$$I(x) \to \frac{f_z(x)}{1 - \int_0^x S_R(x-z|z)dF_z(z)}$$

Thus, *P(x)* and *I(x)* reduces to cumulative probability $F_Z(x)$ and hazard $f_Z(z)/S_Z(x)$ when $S_R(x|z)=1$, but not in general.

3.2. Screening-related P and I

The results in [3a]-[3d] describe the outcome in a population where the states of the individuals are continuously supervised. When the health states of the individuals are examined at discrete times, say at screenings performed every s:th year, then it can only be assessed whether the onset of the disease has occurred during the preceeding screening interval or not. Provided that all disease states are correctly classified (sensitivity and specificity are 1), the random variable Z has now to be replaced by ZD, where ZD=is for is-i<Z≤is, i=1,2,... . By inserting ZD for Z in [4]-[6] one obtaines, after integration by parts, the following expressions for screening-related P and I:

$$P_{nm}(s) = \sum_{i \geq 1} \left[F_Z(is) - F_Z(is-s) \right] \int_{is}^{\infty} f_V(u) S_R(u-is|is) du \qquad [7]$$

$$P_{tot}(s) = \frac{P_{nm}(s)}{\left(\sum_{i \geq 1} \left[F_Z(is) - F_Z(is-s) \right] F_V(is) + P_{nm}(s) + S_Z(\infty) \right) p_M + 1 - p_M} \qquad [8]$$

$$I(s) = \frac{\sum_{i \geq 1} \left[F_Z(is) - F_Z(is-s) \right] f_V(is)}{\sum_{i \geq 1} \left[F_Z(is) - F_Z(is-s) \right] F_V(is) + S_Z(\infty)} \qquad [9]$$

3.3. Illustrations of the results

Only for the purpose of illustrating the results, consider the following situation: The cross section of times spent in the population have the density $f_V(x)=exp(-x/\mu_V)/\mu_V$, where μ_V is the mean. The times from the entrance into the population until the onset of the disease have the cdf $F_Z(x)=\pi(1-exp(-x/\mu_Z))$, where $\pi=F_Z(\infty)$ is the probability that an individual will eventually be diseased. The two functions $f_V(x)$ and $F_Z(x)$ are plotted in Figure 1 when $\mu_V=\mu_Z=10$ and $\pi=0.2$. For simplicity, only the case when the disease is mortal for a proportion p_M of the population is considered. The sf of the times to death from the onset of the disease is $S_R(x|z)=exp(-x/\mu_R)$ independently of z, where μ_R is the mean.
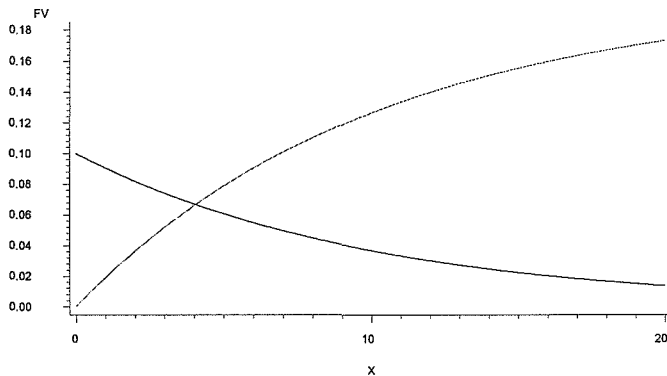
Figure 1. *Decreasing curve:The relative frequencies of times spent in the population for a cross section of individuals, given by $f_V(x) = \exp(-x/10)/10$. Increasing curve: Cumulated risk of the disease, increasing with time spent in the population, given by $F_Z(x) = 0.2(1-\exp(-x/10))$.*

From (4) - (6) one obtains

$$P_{tot} = \frac{\pi}{\left(1+\dfrac{\mu_V}{\mu_R}\right)\left(1+\dfrac{\mu_Z}{\mu_V}\right) - \pi \cdot p_M \cdot \dfrac{\mu_V}{\mu_R}}, \quad I = \frac{\pi}{\mu_Z + (1-\pi)\mu_V}$$

For instance, if $\pi = 0.2$ and $\mu_Z = \mu_V = 10$ then $I = 0.011$, and if furthermore $p_M = 0.9$ and $\mu_R = 5$ then $P_{tot} = 0.050$. Notice that $P_{tot} \to 0$ as $\mu_R \to 0$, while $P_{tot} \to \pi(1 + \mu_Z/\mu_V)^{-1}$ as $\mu_R \to \infty$, the largest value of the prevalence.

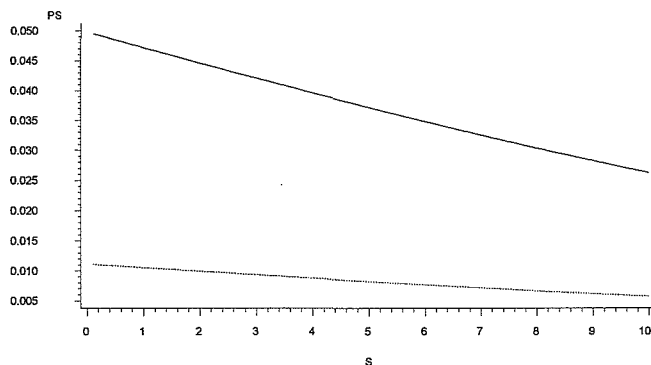Now, consider the screening-related P and I. The infinite sums in [8] and [9] can can be expressed

$$P_{tot}(s) = \left\{ p_M (1 + \frac{1}{I(s)}\left(\frac{1}{\mu_V} + \frac{1}{\mu_R}\right)) + \frac{(1-p_M)}{\pi}\left(1 + \frac{\mu_V}{\mu_R}\right)\frac{(g(s)-1)}{(\exp(s/\mu_Z)-1)} \right\}^{-1}$$

$$I(s) = \frac{\pi(\exp(s/\mu_Z)-1)}{\mu_V(g(s)-1-\pi(\exp(s/\mu_Z)-1))}$$

where $g(s) = \exp(s(1/\mu_Z + 1/\mu_V))$.

$I(s)$ and $P_{tot}(s)$ are shown in Figure 2 as functions of s when $\pi = 0.2, \mu_Z = \mu_V = 10, \mu_R = 5$ and $p_M = 0.9$.

Figure 2. *Screening-related P (upper curve) and I (lower curve) in the illustrative example.*

When the screening interval s tends to zero, $I(s)$ and $P(s)$ tend to I and P, respectively. With increasing screening interval, $I(s)$ and $P(s)$ will decrease as a result of the fact that diseased induviduals will leave the population without being detected. Notice the roughly linear behaviour of the two functions.

4. Optimized sceduling of screenings

When the population consists of subgroups with different P's and I's, the problem arises of how to chose the screening interval s within each subgroup in order to maximize the total proportion of detected cases. Evidently, subgroups with high P or I should be screened more often. Here, a solution of the problem will be given which is based on the assumption that P and I are roughly linear functions of the screening interval s (cf. Figure 2.).

Let π_i be the proportion of the i:th subgroup and let $a_i - b_i s_i$ be the corresponding I, assumed to be linear and based on the screening interval s_i. The total I in the population is

$$I(s_1 \ldots s_i \ldots) = \sum_i \pi_i (a_i - b_i s_i) \qquad [10]$$

Assume further that resources are limited, so only a fraction p of the total population can be screened every year. With N_i individuals in the i:th

subgroup, this means that (N_i/s_i) from the latter can be screened every year and $p = \sum_i (N_i / s_i) / \sum_i N_i$, or

$$p = \sum_i \frac{\pi_i}{s_i} \qquad [11]$$

Maximizing [10] with respect to the s_i's , subject to [11] yields the optimal solutions of the screening intervals

$$s_i^* = \frac{\sum_i \pi_i \sqrt{b_i}}{p\sqrt{b_i}}, \text{ and } I(s_1^* \ldots s_i^* \ldots) = \sum_i \pi_i a_i - \frac{\left(\sum_i \pi_i \sqrt{b_i}\right)^2}{p} \qquad [12]$$

With equal screening intervals, $s_i = s$ for all subgroups and in this case

$$s = \frac{1}{p}, \text{ and } I(s \ldots s \ldots) = \sum_i \pi_i a_i - \frac{\sum_i \pi_i b_i}{p} \qquad [13]$$

The gain by using optimal rather than equal screening intervals can be judged by comparing the different expressions for I in [12] and [13]. Similar results can be derived for P, provided that the latter is linearly decreasing with s.

Above, a linear form for I was assumed. One may instead maximize e.g. polynomials of the second order subject to [11], but the linear form is simpler and has been found to be realistic in many practical situations. How P and I can be estimated in practice from screening data is demonstrated in the next section.

5. An application: Screening for diabetic retinopathy

Proliferative diabetic retinopathy (PDR) is a disease among diabetic patients which unlikely is detected without screening [SUS 82]. A total number of 700 patients with type 1 diabetes mellitus were screened for PDR at Sahlgren's Hospital, Gothenburg, Sweden [KAL 93]. Two groups of patients at risk of PDR were identified: 90% with no- or background retinopathy (0-BDR) and 10% with pre-PDR (pre-PDR). The estimated risk of developing PDR, i.e. estimates of F_z (x), for the two groups is shown in Figure 3. The risk increases with the duration of the diabetes above 10 years, and the risk is roughly 4-5 times higher for patients with pre-PDR. Figure 4 shows a histogram based on a cross section of 699 durations spent in the risk set. This histogram will be used as an estimate of $f_v(x)$ in both subgroups since it was not possible to obtain separate histograms for the two subgroups

from the available data set. Neither it was possible to estimate the function $S_R(x|z)$ from the data and therefor PDR will be considered as a disease which is non-mortal with $S_R (x|z)=1$ for all x,z. In this case the expressions in [7] and [9] simplifies:

$$P_{nn}(s) = \sum_{i \geq 1} \left[F_z(is) - F_z(is-s) \right] S_V(is), \qquad [14]$$

$$I(s) = \frac{\sum \left[F(is) - F_z(is-s) \right] f_V(is)}{1 - P_{nn}(s)} \qquad [15]$$
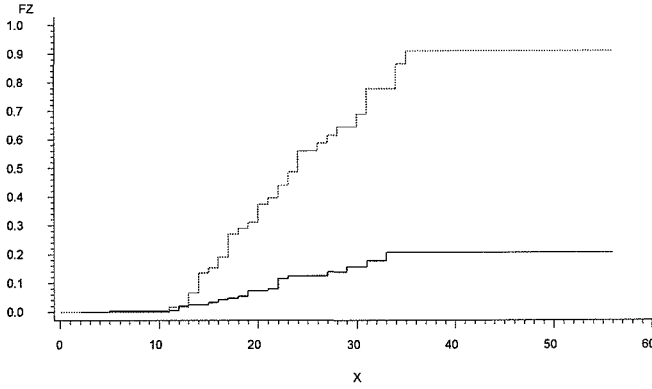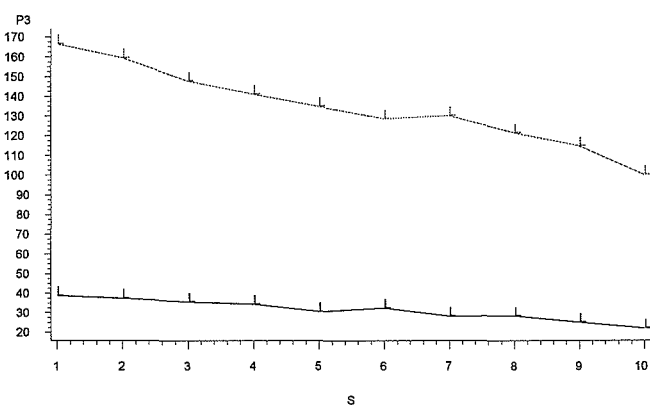

Figure 3. *Cumulated risk of PDRwith increasing duration of diabetes for the 0-BDR group (lower curve) and for the pre-PDR group (upper curve)*

FU
0.06
0.05
0.04
0.03
0.02
0.01
0.00

0   10   20   30   40   50   60

X
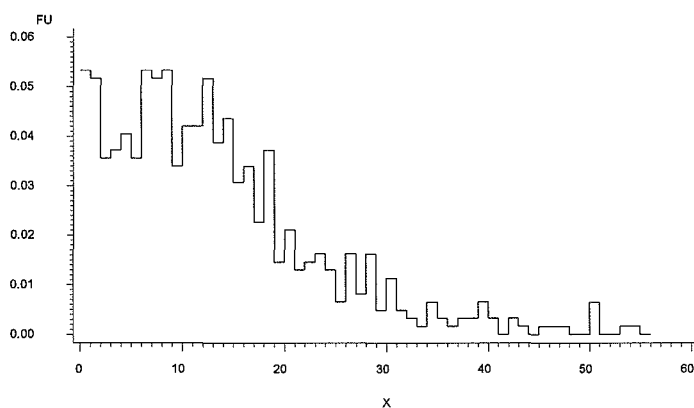
Figure 4. *Histogram (relative frequency within intervals of one year) showing the duration of diabetes in a cross section 699 patients.*

The computation of $P_{nm}(s)$ and $I(s)$ from the empirical estimates of $F_Z(x)$ and $f_V(x)$ shown in Figure 3 and 4 are somewhat heavy and require the use of a computer. Figure 5 and 6 show the estimates of $P_{nm}(s)$ and $I(s)$ for the two groups of patients. The computations were carried out for $1 \leq s \leq 10$, performed by a program written in SAS® (which can be offerred from the author on request).

P3
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20

1   2   3   4   5   6   7   8   9   10

S

Figure 5. *Estimated sreening-related prevalence, $P_{nm}(s)$, for the 0-BDR group (lower curve) and for the pre-PDR group (upper curve).*
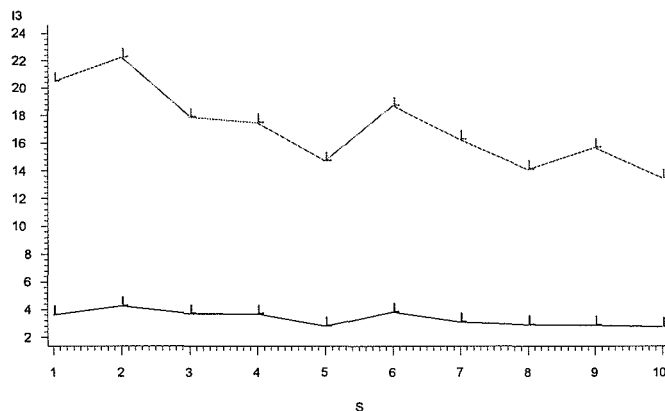
Figure 6. *Estimated screening-related incidence, I(s), for the 0-BDR group (lower curve) and for the pre-PDR group (upper curve).*

Estimated straight lines are

$$P(s) = \begin{cases} (42 - 1.8s) \cdot 10^{-3} & \text{for } 0\text{-BDR} \\ (175 - 7.5s) \cdot 10^{-3} & \text{for pre-PDR} \end{cases}$$

$$I(s) = \begin{cases} (4 - 0.14s) \cdot 10^{-3} & \text{for } 0\text{-BDR} \\ (22 - 0.9s) \cdot 10^{-3} & \text{for pre-PDR} \end{cases}$$

Estimates of the "true" values of P and I, which would have been obtained with continuous screening, are obtained by putting s=0 in the estimated straight lines. The optimal screening intervals for the two groups, determined from [12] are $s^* = 1.10/p$ for 0-BDR and s* =0.54/p for pre-PDR. In the latter, the coefficients from P(s) were used. The coefficients from I(s) give roughly the same answer: Patients with pre-PDR should be screened roughly twice as often as patients with 0-BDR in order to maximize the total number of detected cases in the total population. This advice should be regarded as a general recommendation used for the planning of the screenings. The final choice of screening intervals will depend on p, i.e. on the resources available at the hospital, and on individual risks.

6. Conclusions

It has been shown how prevalence and incidence in open dynamic populations can be estimated from screenings. The results are especially

useful in countries with limited medical resources, where screening examinations often are the only way of receiving knowledge about the true medical state of the population, but also in countries where medical resources are believed to be sufficient. In the latter, there is still a hugh spectrum of diseases which in most cases only can be detected by screening examinations, such as diabetic retinopathy and many neuronial diseases.

It has also been shown how screenings can be planned to achieve optimal solutions under limited resources. These results can be used to reduce the costs and still maintain the quality of a screening study.

Acknowledgements

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APPENDIX

Some fundamental results for the functions describing the state of the population

The derivations make use of the following lemma about Poisson shot noice processes (cf. Papoulis, 1965, pp. 562-576):

Lemma Let $A_t(x)$ be the counting function on the time interval $(t, t+x)$ of a Poisson process with intensity λ and let $\{U_i\}$ be the sequence of times measured from t until the i:th event occurs. Put

$$\delta(x - U_i) = \begin{cases} 1 & \text{with probability } p(x - U_i) \\ 0 & \text{-"-} \quad 1 - p(x - U_i) \end{cases}$$

Then $\displaystyle\sum_{i \leq A_t(x)} \delta(x - U_i)$ has a Poisson distribution with mean $\displaystyle\lambda \int_0^x p(u)\,du$.

To prove the relations in [3a], notice that $L = \displaystyle\sum_{i \leq A_{t-y}(y)} \delta(y - U_i)$ as $y \to \infty$.

For non-mortal diseases, $\delta(y-U_i)=1$ if $T_i > y-U_i$ and thus, $p(u)=P(T_i>u)=S_T(u)$. For mortal diseases, $\delta(y-U_i)=1$ if $\min(T_i, Z_i+R_i)>y-U_i$ and from this it follows that $p(u)= P(\min(T_i, Z_i+R_i)>u)= S_T(u)S_{Z+R}(u)$, where

$$S_{Z+R}(u)=P(Z+R>u, Z>u)+P(Z+R>u,\ Z\leq u)=S_Z(u)+\int_0^u S_R(u-z|z)\,dF_Z(z).$$

LH can be represented in a similar way as L, but now $\delta(y-U_i)=1$ if $T_i>y-U_i$ and $Z_i>y-U_i$. Since $p(u)=P(T_i>u, Z_i>u)=S_T(u)S_Z(u)$, [3b] follows. [3c] is proved analogously.

In [3d] $N(x) = N(t-y,t,x)+N(t,t+x,x)$ as $y\to\infty$, where the latter two terms are defined in Section 2. Now,

$$N(t-y,t,x)=$$

$$\sum_{i \leq A_{t-y}(y)} \delta(y - U_i), \text{ where } \delta(y - U_i) = 1 \text{ if } T_i > Z_i \text{ and } y - U_i < Z_i < y - U_i + x$$

$$N(t, t + x, x) =$$

$$\sum_{i \leq A_t(x)} \delta(x - U_i), \text{ where } \delta(x - U_i) = 1 \text{ if } T_i > Z_i \text{ and } Z_i < x - U_i$$

From the Lemma it now follows that the expectation of N(x) is

$$\lambda \int_0^\infty \int_u^{x+u} S_T(z)\,dF_Z(z)\,du + \lambda \int_0^x \int_0^u S_T(z)\,dF_Z(z)\,du$$

and it is easily veryfied that the expression above is the same as the one in [3d].

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1996:4	Wessman, P.	Evaluation of univariate surveillance procedures for some multivariate problems.
1996:5	Särkkä, A.	Outlying observations and their influence on maximum pseudo-likelihood estimates of Gibbs point processes.
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1997:2	Pettersson, M.	Monitoring a Freshwater Fishpopulation: Statistical Surveillance of Biodiversity.