ELSEVIER

European Journal of Cancer 40 (2004) 2474–2479

European Journal of Cancer

www.ejconline.com

A gene-environment interaction between occupation and *BRCA1/BRCA2* mutations in male breast cancer?

Domenico Palli [a,*], Giovanna Masala [a], Renato Mariani-Costantini [b], Ines Zanna [a], Calogero Saieva [a], Francesco Sera [a], Adriano Decarli [c], Laura Ottini [d]

[a] *Molecular and Nutritional Epidemiology Unit, CSPO, Scientific Institute of Tuscany, Via di San Salvi 12, 50135 Florence, Italy*
[b] *Department of Oncology and Neurosciences, University ''Gabriele D'Annunzio'', Chieti, Italy*
[c] *Medical Statistics and Biometry Section, University of Brescia, Brescia, Italy*
[d] *Department of Experimental Medicine and Pathology, University ''La Sapienza'', Rome, Italy*

Received 17 March 2004; received in revised form 21 June 2004; accepted 16 July 2004
Available online 11 September 2004

Abstract

The association of male breast cancer (MBC) with a positive breast cancer (BC) family history and with *BRCA1/2* germ-line mutations points to a genetic component; a relationship with occupation has also been reported. Recently, we identified pathogenetic *BRCA1/2* mutations in a population-based series of Italian MBC patients: here in, we investigated interactions between a carrier status for *BRCA1/2* mutations and occupation using a case–case design and estimating case-only odds ratios (CORs). Truck-driving was the most frequent occupation (3/4 *BRCA*-related cases and 2/19 unrelated cases). An interaction between carrier status and working as a truck-driver emerged, when we classified MBC cases as ''ever/never-held'' this job title (COR 25.5; 95% Confidence Limits (CL): 1.1–1,412.5) or according to truck-driving as the ''longest-held'' work (COR 54.0; 95% CL: 1.6–2,997.5). The possible modifying effect on MBC risk in subjects carrying *BRCA1/2* germ-line mutations of an occupation characterised by exposure to chemicals such as polycyclic aromatic hydrocarbons (PAH) that are capable of inducing DNA damage, may provide clues to the role of environmental exposures in modifying BC risk in mutation carriers in both genders.

Keywords: Male breast cancer; *BRCA1*; *BRCA2*; Occupation; Gene-environment interaction; Polycyclic aromatic hydrocarbons

1. Introduction

Male breast cancer (MBC) is rare compared with female breast cancer (FBC). In Western countries, FBC is the most commonly diagnosed malignancy among women, while MBC accounts for less than 1% of all cancers in men. It is generally accepted that breast cancer represents the same disease entity in both genders. However, the current knowledge on FBC risk factors, involving primarily reproductive and hormonal factors, cannot be readily transferred to males, since MBC occurrence obviously cannot be related to the female hormonal and reproductive factors involved in the aetiology of FBC. By contrast, epidemiological studies on the determinants of MBC are not confounded by hormonal and reproductive factors and could provide clues to the environmental causes of BC, such as exposure(s) to occupational carcinogens.

The consistently reported association of MBC risk with a positive family history of breast cancer points to a relevant genetic component in disease predisposition [1]. Evidence provided by several studies implicates pathogenetic germ-line mutations of *BRCA2* and, at a lower frequency, of *BRCA1* in MBC, and possibly other

* Corresponding author. Tel.: +39 055 626 8360; fax: +39 055 679 954.
E-mail address: d.palli@cspo.it (D. Palli).

0959-8049/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.ejca.2004.07.012

susceptibility genes. Mutations in *BRCA1* and *BRCA2* were estimated to be responsible for 16% and 76%, respectively, of the MBCs occurring in high-risk breast/ovarian cancer families [2,3].

MBC has been associated with advancing age, primary and secondary hyperoestrogenism, and Klinefelter's syndrome. Several studies have addressed the relationship between occupational exposures and MBC, suggesting an association with ionising radiations, high temperatures and extremely low electromagnetic fields [4]. Furthermore, an increased MBC risk has been reported in occupational groups exposed to engine exhaust and gasoline combustion products [5–7], an environmental exposure that has also been associated with an increased FBC risk [8]. Most of these studies were case-control studies due to the rarity of disease, but a few cohort studies focusing on occupational exposures have also provided results. In general, no detailed information on the family history of breast cancer and other malignancies was collected.

Some observations suggest that exogenous exposures could modify the risk of developing *BRCA* related-tumours [9]. Environmental and life-style factors, particularly occupational carcinogen exposures, could possibly contribute to the MBC risk and interact with genetic characteristics.

We have recently estimated the prevalence of pathogenetic *BRCA1/2* mutations in a well-characterised population-based series of 25 MBC patients from Florence, Central Italy; constitutional *BRCA1/BRCA2* mutations accounted for 16% (4/25) of our male breast cancer cases [10]. A detailed occupational history of these MBC cases has been collected with the aim of evaluating a possible interaction between a carrier status for *BRCA1/BRCA2* mutations and occupation reported at interview.

2. Patients and methods

A detailed description of the study protocol has been reported in our previous report in Ref [10]. Briefly, we have identified a series of MBC cases newly-diagnosed in the area of Florence in the period 1990–1998. After exclusion of those who were deceased and patients who had migrated, the remaining subjects were traced and invited to participate in the study. Overall, a series of 31 unrelated MBC patients were contacted; six cases refused to participate, mostly because of advanced age or because they were severely ill. Twenty-five cases agreed to participate and signed an informed consent with a detailed description of the study protocol including information about the mutational analysis of *BRCA1* and *BRCA2*. The entire coding sequence of the two genes was analysed by using Protein Truncation Test and Single Strand Conformational Polymorphism assay, followed by sequencing [10]. Each subject provided: (1) a blood sample; (2) detailed information on his personal history of cancer at any site; (3) detailed information on his family history for cancer at any sites, including all first- and second-degree relatives of both genders (with particular attention to breast and ovarian cancers); (4) a detailed smoking history (including age at start, number of cigarettes smoked per day, age at quitting). A detailed working history up to the date of BC diagnosis was also collected for 23 out of 25 subjects, including the starting and ending year for each job reported, the main activity of the company where the subject worked and a brief description of the tasks carried out at his workplace. The mean number of jobs reported at interview was 2.0 (11 subjects reported only one job and a subject reported five different jobs). For each subject, we identified the occupation that they had held for the longest period of time (''longest-held'') and all other jobs that they had ''ever-held''.

The existence of interactions between carrier status for *BRCA1/BRCA2* and occupations was investigated using a case–case design. Study subjects were classified according to a specific occupation (yes/no or ever/never), potentially associated with exposure to carcinogens of interest, and according to mutational carrier status (present/absent) either in a 2×2 table or in a logistic model including a term for age. The case-only odds ratios (CORs) and 95% Confidence Limits (CLs) were computed as a measure of gene-environment interactions that can only be interpreted as a departure from a multiplicative effect between the exposure and the genotype [11]. The case-case design does not allow us to assess the independent effects of the exposure alone or the genotype alone [11].

Table 1
Distribution of occupations reported at interview (as ''longest-held'' or ''ever-held'') in a series of 23 male breast cancer cases (Florence, Italy)

Occupation	Longest-held *N* (%)	Ever-held *N* (%)
Truck-driver	4 (17)	5 (11)
Farmer	2 (9)	4 (9)
Textile worker	2 (9)	3 (7)
Storekeeper	2 (9)	3 (7)
Army	2 (9)	2 (4)
Construction worker	1 (4)	3 (7)
Shopkeeper/assistant	2 (9)	2 (4)
Land surveyor	1 (4)	1 (2)
Industrial machinery fitter	1 (4)	2 (4)
Lawyer	1 (4)	1 (2)
Clerk	1 (4)	1 (2)
University teacher	1 (4)	1 (2)
Electroplater	1 (4)	1 (2)
Wholesale dealer	1 (4)	1 (2)
Pharmacist	1 (4)	1 (2)
Other	–	15 (33)
Total	23	46

3. Results

In this population-based series of MBC cases, four *BRCA1/BRCA2* mutation carriers (4/25, 16%) were identified [10]. In particular, mutational screening of the entire coding sequence of these two genes revealed four pathogenetic germ-line mutations, one in *BRCA1* (*BRCA1* 3345delAG) and three in *BRCA2* (*BRCA2* 1003delA, *BRCA2* 6010G > T, *BRCA2* 6696delTC).

A detailed working history was available for 23 of the 25 study subjects. The mean age at diagnosis was 65.8 years (range 42–87 years). The distribution of the ''longest-held'' occupation and jobs ''ever-held'' are shown in Table 1. The ''longest-held'' occupation most frequently reported was truck-driver; all other jobs were reported by only one or two individuals, thus precluding any analyses for the other occupations. In addition for the ''ever-held'' analysis, truck-driving was again the job that was most frequently reported.

Four subjects reported truck-driving as their ''longest-held'' job (range 18–31 years); in addition another subject reported having worked as truck-driver for six years, although his longest occupation was as a storekeeper. Thus, overall, 5/23 subjects reported to have ''ever'' been employed as truck-driver (22%).

The ''ever-held'' prevalence of truck-driving was 75% (3/4) among the four mutation carriers, and 11% (2/19) in 19 non-mutation carriers, thus leading to an estimated case-only odds ratio of 25.5 (95% exact CL 1.1–1,412.5; Table 2(a)). The age-adjusted COR was 33.0 (95% CL 1.4–752.6). We also calculated the same association measure classifying all MBC cases according to truck-driving as the ''longest-held'' occupation (three subjects among the 4 mutation carriers, 1 among the 19 non-mutation carriers): the resulting COR estimate increased to 54.0 (95% exact CL 1.6–2,977.5; Table 2(b)).

Among the five truck-drivers, the three MBC cases carrying a pathogenetic *BRCA 1/2* germ-line mutation were diagnosed at 53, 60 and 63 years of age and reported to have worked as truck-drivers for 30, 20 and 31 years, respectively; in contrast, the two MBC cases without evidence of *BRCA 1/2* germ-line mutations were both diagnosed at 70 years of age and reported shorter durations (6 and 18 years).

All three *BRCA*-related MBC cases with a long-term history of truck-driving also reported a positive first-degree family history of breast or ovarian cancer: (i) the *BRCA2* 6696delTC carrier had a sister with an ovarian cancer diagnosed at 62 years; (ii) the *BRCA1* 3345delAG carrier had two sisters with BC (at 45 and 41 years); (iii) the *BRCA2* 6010G > T carrier had three sisters with BC. An updated follow-up of these three patients allowed us to identify two additional female relatives diagnosed with cancer of the ovary (one of the sisters of the *BRCA1* 3345delAG carrier already affected with BC) and BC (a fourth sister of the *BRCA2* 6010G > T carrier, diagnosed at 53 years). The fourth *BRCA*-related MBC case (*BRCA2* 1003delA) was diagnosed at 64 years, did not report a family history of breast or ovarian cancer and had worked as shop assistant for 42 years.

According to the information on smoking history collected at interview, 9/25 (36%) cases were classified as current smokers at diagnosis, 12/25 (48%) as former smokers and 4/25 (16%) as never smokers. Among the four BRCA-related MBC cases, two were current smokers and two former smokers: all had started smoking

Table 2
Association between *BRCA1/2* mutation carrier and occupation of a truck-driver: (a) ''ever/never-held''; (b) ''longest-held'' occupation yes/no) in a population-based series of 23 male breast cancer cases; CORs and 95% exact CLs (Florence, Italy)

(a) ''*Ever-held*''

"Ever-held"		Germline *BRCA1/BRCA2* Mutation		Total
		Yes	No	
Truck Driver	Ever	3	2	5
	Never	1	17	18
	Total	4	19	23

COR= 25.5 (95% exact CL: 1.1-1,412.5)

COR = 25.5 (95% exact CL: 1.1–1,412.5)

(b) ''*Longest-held*'' *occupation*

"Longest-Held" Occupation		Germline *BRCA1/BRCA2* Mutation		Total
		Yes	No	
Truck driver	Yes	3	1	4
	No	1	18	19
	Total	4	19	23

COR= 54.0 (95% exact CL: 1.6-2,997.5).

COR = 54.0 (95% exact CL: 1.6–2,997.5)

between 15 and 20 years of age and, at diagnosis, reported a cumulative exposure of 15, 35, 72 and 96 pack-years. Additional details on the whole series of 25 MBC cases (including histopathology) are reported in Table 1 of Ref. [10].

4. Discussion

We have identified a possible gene-environment interaction between an occupational exposure and *BRCA1/2* germ-line mutations in a relatively small population-based series of MBC cases, by measuring the association between mutational carrier status and occupation in a case-only study. A strong approximately 25-fold interaction with working as a truck-driver emerged when we classified subjects as ''ever/never-held'' this specific job title. This association was confirmed and actually became more evident when we carried out analyses stratified by age or classified our study subjects according to their ''longest-held'' job. The results of our analysis can only be interpreted as a departure from a multiplicative effect for the two factors combined: this means that the joint effect of the two characteristics (*BRCA1/2* mutations and truck-driving) on MBC risk is 25-fold higher than the independent effect of the genotype alone multiplied by the independent effect of the exposure alone. The independent effects of the genotype alone or the exposure alone cannot be estimated in this case-only study [11].

For all three *BRCA* -related MBC cases reporting to have worked as truck-drivers, the duration of this occupation was at least 20 years, while they were diagnosed at a younger age than the median value in this series. All of them also reported a positive family history for breast and/or ovarian cancer.

Overall, the MBC risk has been repeatedly associated with occupations involving exposures to engine exhaust. An increased risk of MBC deaths (with two cases observed, standardised mortality ratio (SMR) 14.36; 95% CL 1.73–51.9) has been reported in a cohort of urban policemen in Rome, Italy, an occupational group exposed to engine exhaust during traffic control [5]. An excess risk of MBC for policemen (SMR 2.90; 95%CL 1.08–7.80) was also reported in a Swedish register linkage study [6]. In a case-control study on MBC, based on 230 cases identified and 12 800 controls randomly selected from the files of the National Danish Pension Fund, an excess risk for breast cancer among men was found, when a lag time of at least 10 years was included in the model, for workers who had potentially been exposed to gasoline and combustion products (odds ratio (OR) = 2.2; 95% CL 1.4–3.6), defined as blue-collar workers who had worked for at least three months in vehicle maintenance, wholesale trade of gasoline or car repair shops [7]. A national United States (US) mortality survey, based on the longest-held occupation, reported a five-fold increased MBC risk for taxi-cab drivers [12], while no association emerged for long-term lorry drivers.

Some epidemiological studies have suggested a possible role of exposure to gasoline and combustion products (including motor vehicle repair) on the breast cancer risk in women [8,13,14]. Components of engine exhaust, including polycyclic aromatic hydrocarbons (PAHs) such as benzo[*a*]pyrene (B[*a*]P), have a carcinogenic effect on the mammary gland in experimental settings [15,16].

Perera et al. [17] reported a higher level of PAH–DNA adducts in breast cancer patients (tumour and non-tumour tissues) than in mammoplasty controls, using ^{32}P-post labelling with propidium iodide (PI) nuclease extraction as the method of detection. A subsequent study, also using the ^{32}P-post labelling method, found similar results [18] in 89 breast cancer cases and 29 reduction mammoplasty patients. A more recent case-control study using benign breast disease patients as controls found that elevated levels of PAH–DNA adducts in breast tissue were significantly associated with case-control status [19]. PAH–DNA adducts were also higher in blood samples obtained from breast cancer cases than from healthy women [20]. We have recently shown that workers who are exposed to traffic, in the Florence area of both sexes (including drivers) have increased levels of DNA-adducts in their peripheral white blood cells [21]. Other studies have suggested a role for metabolic polymorphisms [22] or polymorphisms of DNA repair genes in the modulation of PAH–DNA adducts [23].

Active cigarette smokers are exposed to a large series of human carcinogens, including PAH, and have recently been reported to be at significantly increased risk for female BC in a large prospective study carried out in the US [24], although tobacco smoke has anti-oestrogenic effects. By contrast, the association of cigarette smoking with MBC is not clear and results are controversial [4,25]; it has also been shown that smoking is not associated with BC risk among carriers of BRCA mutations [26]. The smoking history of MBC cases in our series agreed well with available data provided by a population-based series in the same area of Florence [27], although it is interesting that all four BRCA-related MBC cases started smoking at an early age.

The specific role of *BRCA1/2* in breast cancer carcinogenesis is not yet completely understood, but the proteins encoded by these two genes have been implicated in DNA repair [28]. It has been suggested that the risk of hereditary breast and ovarian cancer can be modified by external factors. Hormonal factors related to oestrogen exposure and deprivation have been suggested as possible modifiers of BC risk, particularly in *BRCA1* mutation carriers; furthermore, the role of genotoxic

agents, such as PAHs, that can induce DNA damage cannot be excluded as modifiers of BC risk in *BRCA1/2* mutation carriers [29].

In this case-only study, we found a strong interaction between a specific occupation and the development of breast cancer in male *BRCA1/2* mutation carriers. Our study design allows us to estimate the departure from a multiplicative effect of genotype and exposure, under the assumption of independence between these two factors [11,30]; such an assumption appears to be reasonable in this setting. This is a population-based series of MBC cases, and thus the occurrence of a selection bias in case identification may be considered unlikely, although a few eligible cases refused to participate because they were too old or too ill. While the issue of multiple comparisons might be considered, we actually carried out our analyses focusing on truck-driving, the only frequently reported occupation in this series. In addition, the *a priori* plausibility of the hypothesis we have tested agrees with both experimental and epidemiological studies that support the association we have found.

In conclusion, the identification of a possible modifier effect of an occupational exposure to engine exhaust, and particularly to PAHs, on the breast cancer risk in male *BRCA1/2* mutation carriers may provide clues to the possible role of environmental exposures in modifying cancer risk in mutation carriers of both genders. Overall, this finding is consistent with results of previous epidemiological studies suggesting an association of male breast cancer with occupational exposure to engine exhaust and gasoline combustion products and, although limited by the small size of our series, may add to the knowledge that is being accumulated on the role of PAHs in breast carcinogenesis.

Conflict of interest statement

None declared.

Acknowledgements

The authors wish to thank all of the study participants for their collaboration, Drs. Marco Rosselli del Turco and Maria Grazia Muraca (CSPO, Florence) for their help in contacting patients and helpful comments, and RN Donata Tanzini for personal interviews. The study was supported by a grant of Associazione Italiana per la Ricerca sul Cancro (AIRC, Milan) to L.O. Previous work was supported by an AIRC coordinated grant ''Italian Consortium for Hereditary Breast Cancer'', by MIUR–COFIN 2001, and, in part, by a grant from the Italian Ministry of Research to the Center of Excellence on Aging of the University of Chieti. I.Z. has been supported by a grant of Terry Fox Run-Comitato Italia (Milan). CSPO is supported by Regione Toscana, Italy.

References

1. Lynch HT, Watson P, Narod SA. The genetic epidemiology of male breast carcinoma. *Cancer* 1999, **86**, 744–746.
2. Struewing JP, Hartge P, Wacholder S, et al. The risk of cancer associated with specific mutations of *BRCA1* and *BRCA2* among Ashkenazi Jews. *New Engl J Med* 1997, **336**, 1401–1408.
3. Ford D, Easton DF, Stratton M, et al. Genetic heterogeneity and penetrance analysis of the *BRCA1* and *BRCA2* genes in breast cancer families. The breast cancer linkage consortium. *Am J Hum Genet* 1998, **62**, 676–689.
4. Sasco AJ, Lowenfels AB, Pasker-de Jong P. Review article: epidemiology of male breast cancer. A meta-analysis of published case-control studies and discussion of selected aetiological factors. *Int J Cancer* 1993, **53**, 538–549.
5. Forastiere F, Perucci C, Di Pietro A, et al. Mortality among urban policemen in Rome. *Am J Ind Med* 1994, **26**, 785–798.
6. Pollan M, Gustavsson P, Floderus B. Breast cancer, occupation, and exposure to electromagnetic fields among Swedish men. *Am J Ind Med* 2001, **39**, 276–285.
7. Hansen J. Elevated risk for male breast cancer after occupational exposure to gasoline and vehicular combustion products. *Am J Ind Med* 2000, **37**, 349–352.
8. Petralia SA, Vena JE, Freudenheim JL, et al. Risk of premenopausal breast cancer in association with occupational exposure to polycyclic aromatic hydrocarbons and benzene. *Scand J Work Environ Health* 1999, **25**, 215–221.
9. Rebbeck TR. Inherited predisposition and breast cancer: modifiers of *BRCA1/2* -associated breast cancer risk. *Environ Mol Mutagen* 2002, **39**, 228–234.
10. Ottini L, Masala G, D'Amico C, et al. *BRCA1* and *BRCA2* mutation status and tumor characteristics in male breast cancer: a population based study in Italy. *Cancer Res* 2003, **63**, 342–347.
11. Khoury MJ, Flanders WD. Nontraditional epidemiologic approaches in the analysis of gene-environment interaction: case-control studies with no controls! Am. J. Epidemiol. 1996, **144**, 207–213.
12. Cocco P, Figgs L, Dosomeci M, Hayes R, Linet MS, Hsing AW. Case-control study of occupational exposures and male breast cancer. *Occup Environ Med* 1998, **55**, 599–604.
13. Band PR, Le ND, Fang R, Deschamps M, Gallagher RP, Yang P. Identification of occupational cancer risks in British Columbia. A population-based case-control study of 995 incident breast cancer cases by menopausal status, controlling for confounding factors. *J Occup Environ Med* 2000, **42**, 284–310.
14. Petralia SA, Chow WH, McLaughlin J, Jin F, Gao YT, Dosemeci M. Occupational risk factors for breast cancer among women in Shanghai. *Am J Ind Med* 1998, **34**, 477–483.
15. Ronai Z, Gradia S, el Bayoumy K, Amin S, Hecht S. Contrasting incidence of ras mutations in rat mammary and mouse skin tumors induced by anti-benzo[*c*]phentathrene-3,4 diol-1,2 epoxide. *Carcinogenesis* 1994, **15**, 2113–2116.
16. Jeffy DB, Chirnomas RB, Chen EJ, Gudas JM, Romagnolo DF. Epigenetics of breast cancer: polycyclic aromatic hydrocarbons as risk factors. *Environ Mol Mutagen* 2002, **39**, 235–244.
17. Perera FP, Estabrook A, Hewer A, et al. Carcinogen-DNA adducts in human breast tissue. *Cancer Epidemiol Biomarkers Prev* 1995, **4**, 233–238.
18. Li D, Wang M, Dhingra K, Hittelman WN. Aromatic DNA adducts in adjacent tissues of breast cancer patients: clues to breast cancer etiology. *Cancer Res* 1996, **56**, 287–293.

19. Rundle A, Tang D, Hibshoosh H, et al. The relationship between genetic damage from polycyclic aromatic hydrocarbons in breast tissue and breast cancer. *Carcinogenesis* 2000, **21**, 1281–1289.
20. Gammon MD, Santella RM, Neugut AI, et al. Environmental toxins and breast cancer on Long Island I. Polycyclic aromatic hydrocarbons DNA adducts. *Cancer Epidemiol Biomarkers Prev* 2002, **11**, 677–685.
21. Palli D, Russo A, Masala G, et al. DNA adducts levels and DNA repair polymorphisms in traffic exposed workers and a general population sample. *Int J Cancer* 2001, **94**, 121–127.
22. Rundle A, Tang D, Zhou J, Cho S, Perera FP. The association between glutathione *S*-transferase M1 genotype and polycyclic aromatic hydrocarbon–DNA adducts in breast tissue. *Cancer Epidemiol Biomarker Prev* 2000, **9**, 1079–1085.
23. Tang D, Cho S, Rundle A, et al. Polymorphisms in the DNA repair enzyme XPD are associated with increased levels of PAH–DNA adducts in a case-control study of breast cancer. *Breast Cancer Res Treat* 2002, **75**, 159–166.
24. Reynolds P, Hurley S, Goldberg DE, et al. Active smoking, household passive smoking, and breast cancer: evidence from the California teachers study. *J Natl Cancer Inst* 2004, **96**, 29–37.
25. Petridou E, Giokas G, Kuper H, Mucci LA, Trichopoulos D. Endocrine correlates of male breast cancer risk: a case-control study in Athens, Greece. *Br J Cancer* 2000, **83**, 1234–1237.
26. Ghadirian P, Lubinsky J, Lynch H, et al. Smoking and the risk of breast cancer among carriers of BRCA mutations. *Int J Cancer* 2004, **110**, 413–416.
27. Palli D, Russo A, Decarli A. Dietary patterns, nutrient intake and gastric cancer in a high-risk area of Italy. *Cancer Cause Control* 2001, **12**, 163–172.
28. Tutt A, Ashworth A. The relationship between the roles of BRCA genes in DNA repair and cancer predisposition. *Trends Mol Med* 2002, **8**, 571–576.
29. Narod SA. Modifiers of risk of hereditary breast and ovarian cancer. *Nat Rev Cancer* 2002, **2**, 113–123.
30. Khoury MJ. Genetic epidemiology. In Rothman KJ, Greenland S, editors. *Modern epidemiology*. Philadelphia: Lippincott–Raven, 1998. pp. 609–622.