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SPECIAL ARTICLE

CANCER RISKS FOR AUSTRALIAN WOMEN WITH A BRCA1 OR A BRCA2 MUTATION

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One of the primary purposes of genetic testing for mutations in the BRCA1 and BRCA2 genes in patients with familial breast/ovarian cancer has been to provide accurate advice to at-risk relatives. The provision of such advice has been hampered by a lack of appropriate data regarding the cancer risks. Chen and colleagues recently provided precise estimates of the relative risks of breast and ovarian cancer in almost 2000 kindreds with such mutations ascertained through familial cancer clinics across USA. The baseline incidence of breast cancer is lower in Australia than in North America. The relative risks derived from the study have been combined with Australian baseline incidence data to estimate the absolute short-term and long-term risks of breast and ovarian cancers for Australian carriers of different ages. The results are presented as a series of graphs that may be useful in counselling an unaffected carrier of a specified age. It is of note that the incidence of breast cancer in carriers is high in premenopausal women, but approaches the population incidence in postmenopausal women. Conversely, the incidence of ovarian cancer continues to increase from the age of 40 years. Among carriers of BRCA1 or BRCA2 mutations, the cumulative lifetime risk of developing breast cancer is 50–60% and the equivalent risk of ovarian cancer is 20–40%. An unaffected carrier aged 60 years is at greater risk of developing ovarian cancer than breast cancer. These observations have important implications for genetic counselling and decisions regarding prophylactic surgery.

Key words: breast cancer, ovarian cancer, risk.

Abbreviation: CI, confidence interval.

INTRODUCTION

One of the primary purposes of genetic testing in familial breast/ovarian cancer is to provide accurate information about the risks of developing cancer for relatives.[1] The unaffected relatives shown to carry the family's mutation can then use this information to assist their decision-making regarding risk-reduction strategies or to facilitate such decision-making by their children.

The provision of this information has been hampered by the lack of appropriate data regarding the risks of breast and ovarian cancer among carriers of mutations in the BRCA1 and BRCA2 genes. Early studies probably overestimated the risks because they were derived from research kindreds with a high prevalence of cancer.[2] Subsequent population-based studies may have underestimated the penetrance of mutations in clinic-based families because many affected carriers did not have a family history of cancer and would not have been referred to a familial cancer clinic.[3] Clinic-based studies have often been limited by the comparatively small number of families analysed.[4]

Chen *et al.* recently reported clinical data from almost 2000 kindreds with BRCA mutations ascertained through familial cancer clinics across North America.[5] The size of the study provided precise estimates of relative risks of breast and ovarian cancers. But the study was based on experience in the USA, which has a higher baseline incidence of breast cancer than noted in Australia and New Zealand.[6] Nonetheless, the relative risks derived from this study can be combined with Australian baseline incidence data to estimate the short-term and long-term risks of an Australian carrier developing cancer. These estimates can then be provided to women carrying mutations to assist them in their own decision-making.

METHODS

The age-specific incidence of breast and ovarian cancers among Australian women in the general population during 2001 were obtained from the Australian Institute of Health and Welfare (Figs 1,2).[7] This indicates the risk of a woman of a specific age developing the nominated cancer within the next 12 months. These risks in the general female population are the baseline from which the short-term risks of cancer in carriers of mutations were derived.

The age-specific relative risks of breast and ovarian cancers among American carriers of BRCA1 and BRCA2 mutations that were determined by Chen *et al.* (2006) are also shown in Figures 1 and 2.[5] For a woman of a specific age and with a particular mutation, the relative risk is the degree to which the short-term risk of the nominated cancer is increased. For example, a female BRCA1 carrier in her twenties is 100 times more likely to develop breast cancer in the next year than a woman of the same age from the general population (Fig. 1a). However, a female BRCA1 carrier in her sixties is only three times more likely to develop breast cancer in the next year than her age-matched counterpart.

Although baseline incidences vary in different cultures and ethnic groups, the relative risks reflect the influence of pathogenic

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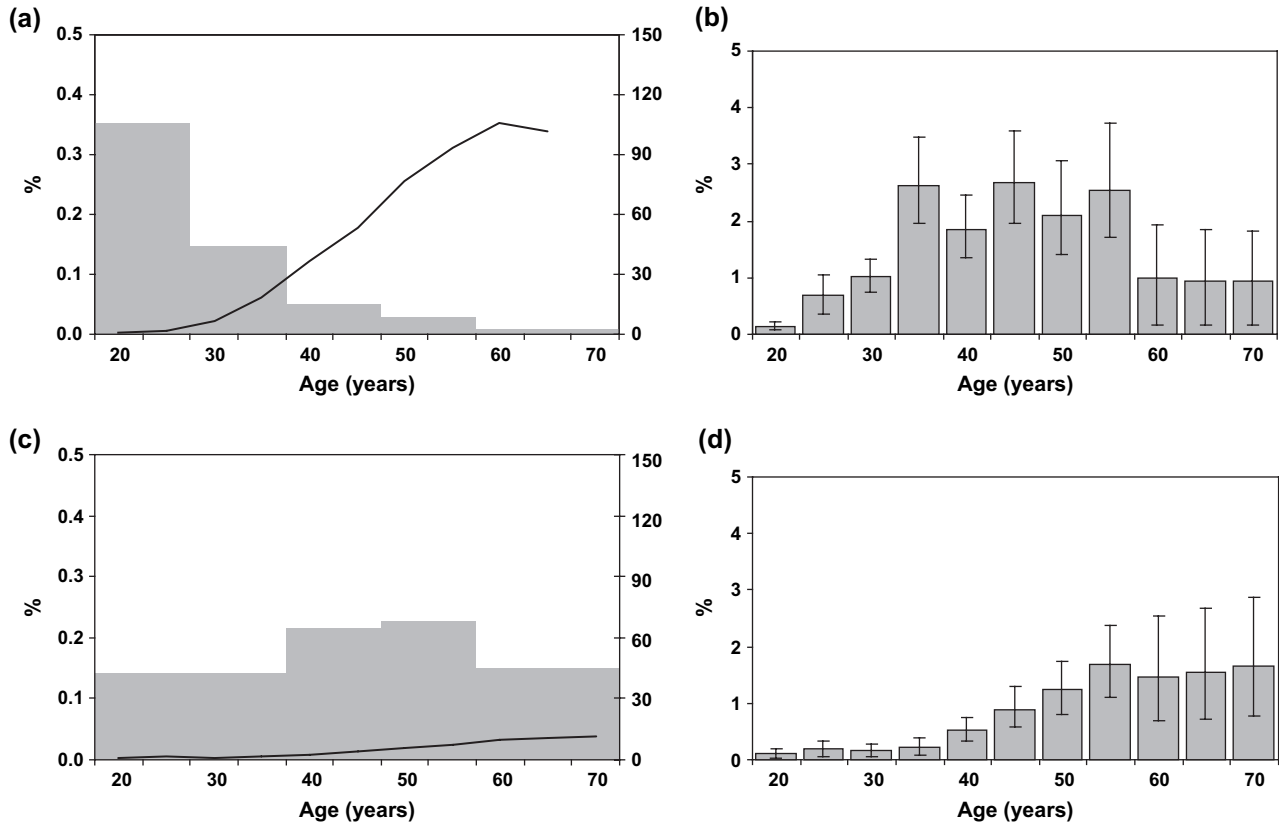

Fig. 1. Annual risk of cancer in BRCA1 carriers. (a) The age-specific baseline risk of breast cancer in the Australian general population (risk per woman per year; left axis) and the age-specific relative risk of breast cancer among BRCA1 carriers (right axis). (b) The age-specific risks of breast cancer (with 95% confidence interval (CI)) among Australian BRCA1 carriers. (c) The age-specific baseline risk of ovarian cancer in the Australian general population (risk per woman per year; left axis) and the age-specific relative risk of ovarian cancer among BRCA1 carriers (right axis). (d) The age-specific risks of ovarian cancer (with 95%CI) among Australian BRCA1 carriers. ▬, relative risk; ——, annual risk.

mutations, which occur in all ethnic groups. The age-specific baseline incidence and the age-specific relative risk were multiplied together to yield the age-specific incidence of a carrier developing the nominated cancer (Figs 1,2). For a carrier of a specific age, this is the short-term risk of her developing the nominated cancer within the next 12 months. The 95% confidence interval (CI) of the relative risk was used to calculate the 95%CI of the annual risk for carriers in each age, cancer and gene category.[5]

These absolute short-term risks in carriers were then applied using the principles of survival analysis to a cohort of unaffected carriers over periods of 10–50 years to determine the long-term cumulative risk of the nominated cancer occurring (Figs 3,4). These long-term risks were calculated for unaffected women aged 20, 30, 40, 50 and 60 years.

RESULTS

Short-term risks of cancer for unaffected carriers

In the Australian general population, the annual risk of breast cancer is consistently much higher than the risk of ovarian cancer. By the age of 70 years, the annual risk of breast cancer in the general population is six times greater than the annual risk of ovarian cancer (Figs 1,2).

In young women carrying BRCA1 and BRCA2 mutations, the relative risk of breast cancer is strikingly raised (50- to 100-fold) (Figs 1a,2a). But this relative risk rapidly declines and by the age of 60 years is less than threefold. The predominant risk of breast cancer is principally among premenopausal women. For a young woman carrying a mutation in either gene, the short-term risk of breast cancer is 1% per year by the age of 30 (Figs 1b,2b). Over the subsequent 30 years, the rising baseline incidence of breast cancer and the declining relative risk due to the mutation combine to maintain her risk of breast cancer at 2–3% per year. But from the age of 60, the risk of breast cancer drops to less than 1% per year.

In contrast, the relative risk of ovarian cancer remains consistently high (30- to 60-fold) throughout adult life (Figs 1c,2c). For young women carrying a mutation in either gene, the high relative risk still corresponds to an annual risk of less than 0.2% because the annual risk in the general female population is very low. But after the age of 40, the annual risk of ovarian cancer rises and it exceeds 1% per year by the age of 50–60 years (Figs 1d,2d). After the age of 60, the annual risk of ovarian cancer exceeds the annual risk of breast cancer for carriers of both BRCA1 and BRCA2 mutations.

Long-term risks of cancer for unaffected carriers

Figure 3 presents the cumulative ('long-term') risks of breast and ovarian cancers for unaffected female BRCA1 carriers of different ages. The equivalent graphs for unaffected BRCA2 carriers are

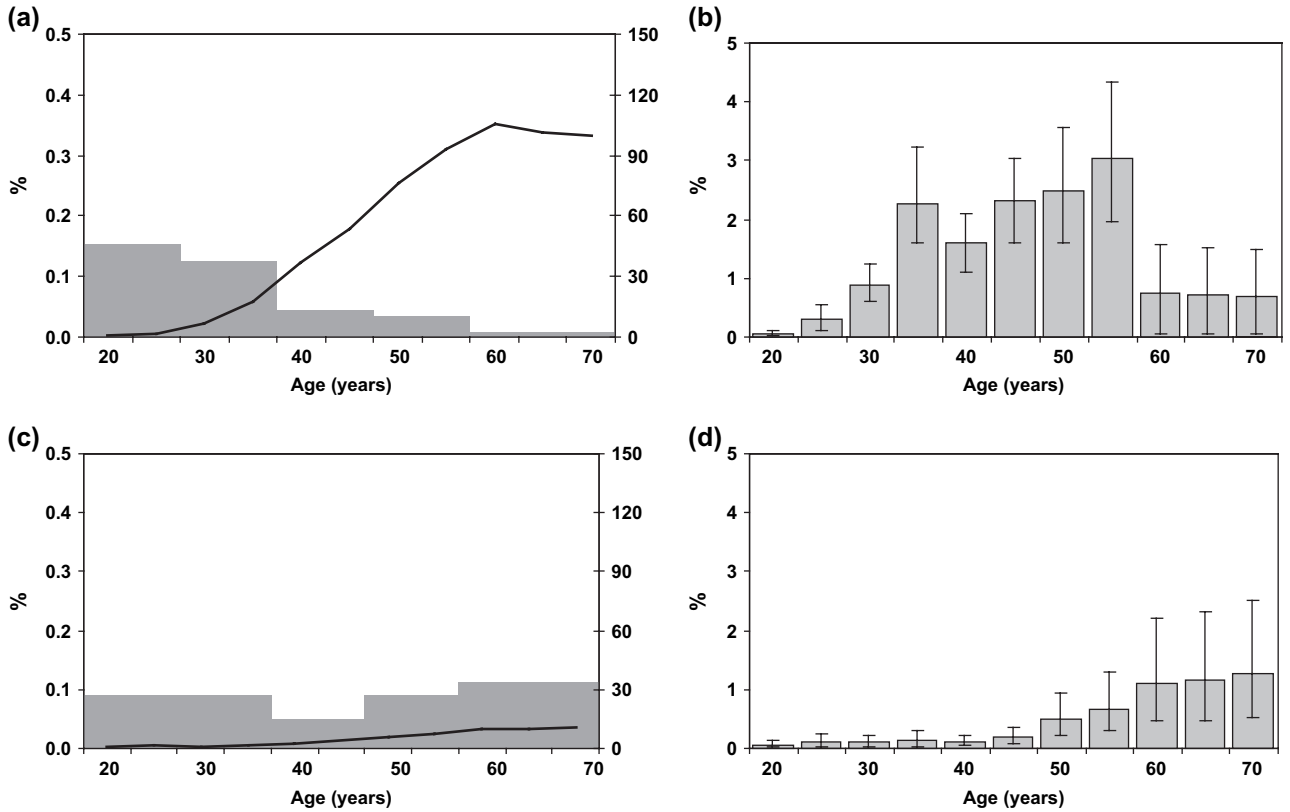

Fig. 2. Annual risk of cancer in BRCA2 carriers. (a) The age-specific baseline risk of breast cancer in the Australian general population (risk per woman per year; left axis) and the relative risk of breast cancer among BRCA2 carriers (right axis). (b) The age-specific risk of breast cancer (with 95% confidence interval (CI)) among Australian BRCA2 carriers. (c) The age-specific baseline risk of ovarian cancer in the Australian general population (risk per woman per year; left axis) and the relative risk of ovarian cancer among BRCA2 carriers (right axis). (d) The age-specific risk of ovarian cancer (with 95%CI) among Australian BRCA2 carriers. ▬, relative risk; ——, annual risk.

presented in Figure 4. For example, the long-term risk of an unaffected BRCA1 carrier aged 20 years developing breast cancer by the age of 70 is almost 60%. Her cumulative risk of developing ovarian cancer by the same age is approximately 40%. For comparison, an unaffected 20-year old woman in the Australian general population has a cumulative risk of 10% of developing either cancer by the age of 70.

If a BRCA1 carrier reaches the age of 40 without having developed either cancer, her risk of subsequently developing breast cancer by the age of 70 years is reduced to 40%. But her risk of developing ovarian cancer is unchanged because the risk of ovarian cancer before the age of 40 years was so low. For an unaffected BRCA1 carrier aged 50 years, the cumulative risk of ovarian cancer over the next 20 years exceeds the equivalent risk of breast cancer.

The age-specific annual risks of both breast and ovarian cancers are similar for carriers of BRCA1 and BRCA2 mutations, but the risks are generally slightly higher for carriers of BRCA1 mutations. As a result, there are differences in the long-term risks of cancer, particularly ovarian cancer, when considered over periods of two or more decades.

DISCUSSION

The presentation of short-term and long-term risks for carriers of different ages may be useful in discussions about the management of these cancer risks, including the place of prophylactic surgery. For example, an unaffected BRCA1 carrier aged 30 years is at 1% risk of developing breast cancer and much less risk of developing ovarian cancer (Figs 1,3). In the longer term, she is at 20% risk of developing breast cancer and 4% risk of developing ovarian cancer by the age of 40 years. She may decide to accept this level of risk in the short term so that she can complete her family and defer a decision regarding prophylactic surgery for a few years. However, an unaffected 60-year-old BRCA1 carrier has little more than the population risk of breast cancer over the next decade, but is at substantially higher risk of developing ovarian cancer. There is little medical indication for prophylactic mastectomy at this age, but a case can be made for considering prophylactic oophorectomy.

There are three technical considerations regarding this analysis. First, the baseline incidence data used in these analyses have not been adjusted to allow for the prevalence of BRCA1 or BRCA2 mutations in the Australian general population. Mutations in BRCA1 and BRCA2 are rare and account for only a small proportion of all breast cancer and hence would have little effect on the baseline incidence data.[8] Second, in the study of Chen *et al*. (2006) there were insufficient observations to estimate the relative risk of ovarian cancer among carriers aged 20–29 years.[5] For this analysis, the relative risk was assumed to be the same as in women carrying the same mutation aged 30–39 years. Finally, and perhaps most importantly, the use of American relative risk data and Australian baseline incidence data is an interim response to the lack of a comprehensive analysis regarding the absolute risks of

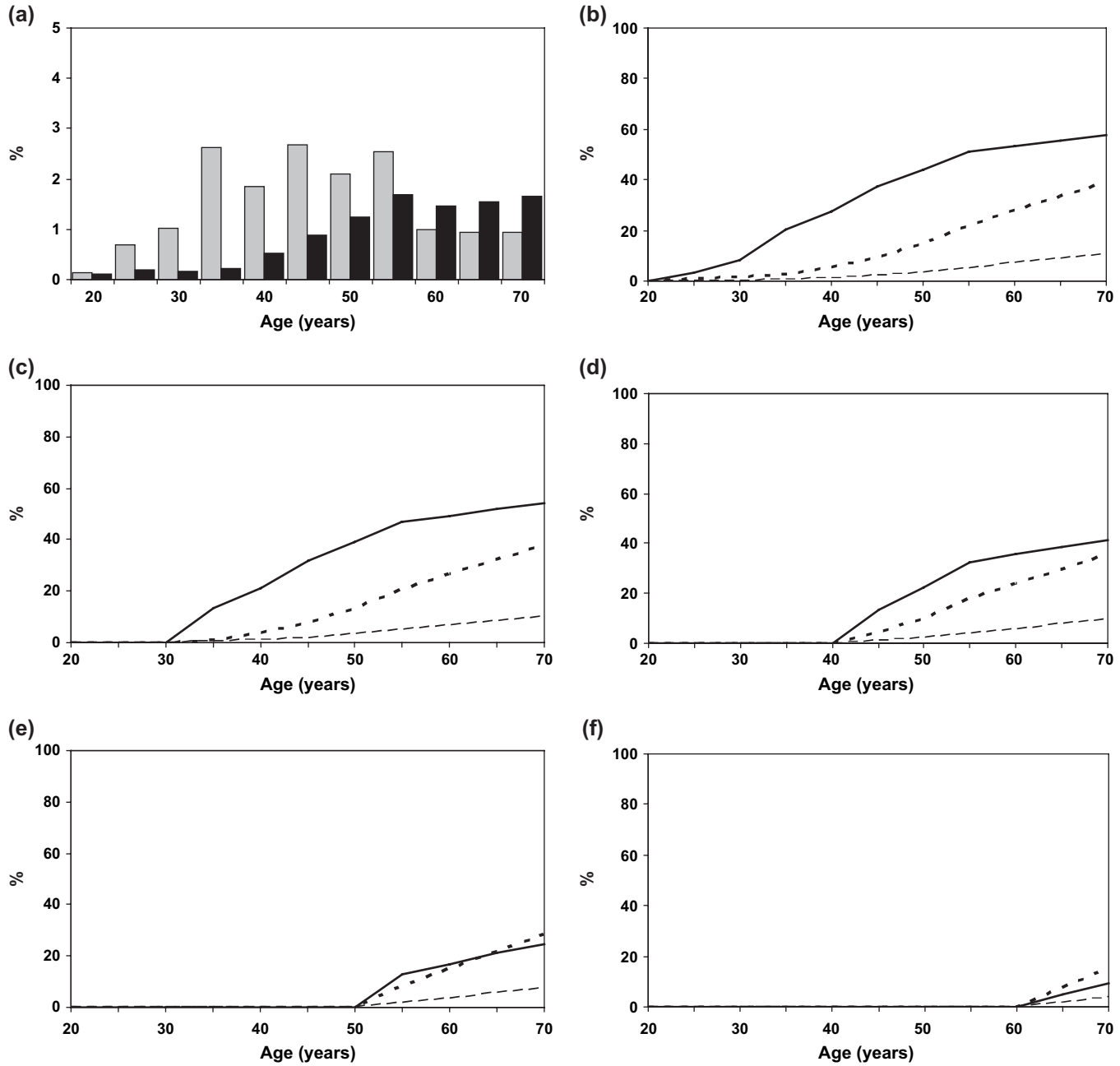

Fig. 3. Short-term and long-term risks of cancer in BRCA1 carriers. (a) The age-specific risks of breast (□) and ovarian (■) cancer (risks per woman per year, that is 'short-term risks') for an Australian female BRCA1 carrier are summarized. The cumulative risks (i.e. 'long-term risks') of breast and ovarian cancers for an unaffected female BRCA1 carrier of different ages; in each case, the cumulative risk of breast or ovarian cancer (combined) for an unaffected woman in the general population is shown for comparison: (b) from 20 years, (c) from 30 years, (d) from 40 years, (e) from 50 years, and (f) from 60 years. ——, breast; - - - , ovary; – – –, population (breast and ovary).

cancer among Australian carriers attending local clinics; the outcome of such studies are awaited with interest.

CONCLUSION

It is clear that the breast and ovarian cancer risks among carriers of BRCA mutations must be considered separately, that mutations in the two genes should not be regarded as equivalent, and that the risks must be tailored to the age of the carrier seeking advice.

Prophylactic surgery is a significant and irreversible step in managing cancer risk. It is strongly recommended that any proposal to embark on such surgery be discussed by a multidisciplinary team providing surgical, gynaecological, psychological and clinical genetic expertise in managing carriers.[9] The provision of these risk data does not eclipse the need for this level of consultation. It is also important to note that, at the worst, the combined annual risk of breast or ovarian cancer among carriers is no more than 4% per year. There is time for discussion and counselling and no place for urgent prophylactic surgery.

These risk figures should be the beginning, not the end, of a discussion about what the best course of action might be for a specific patient. There is a myriad of biological, psychological,

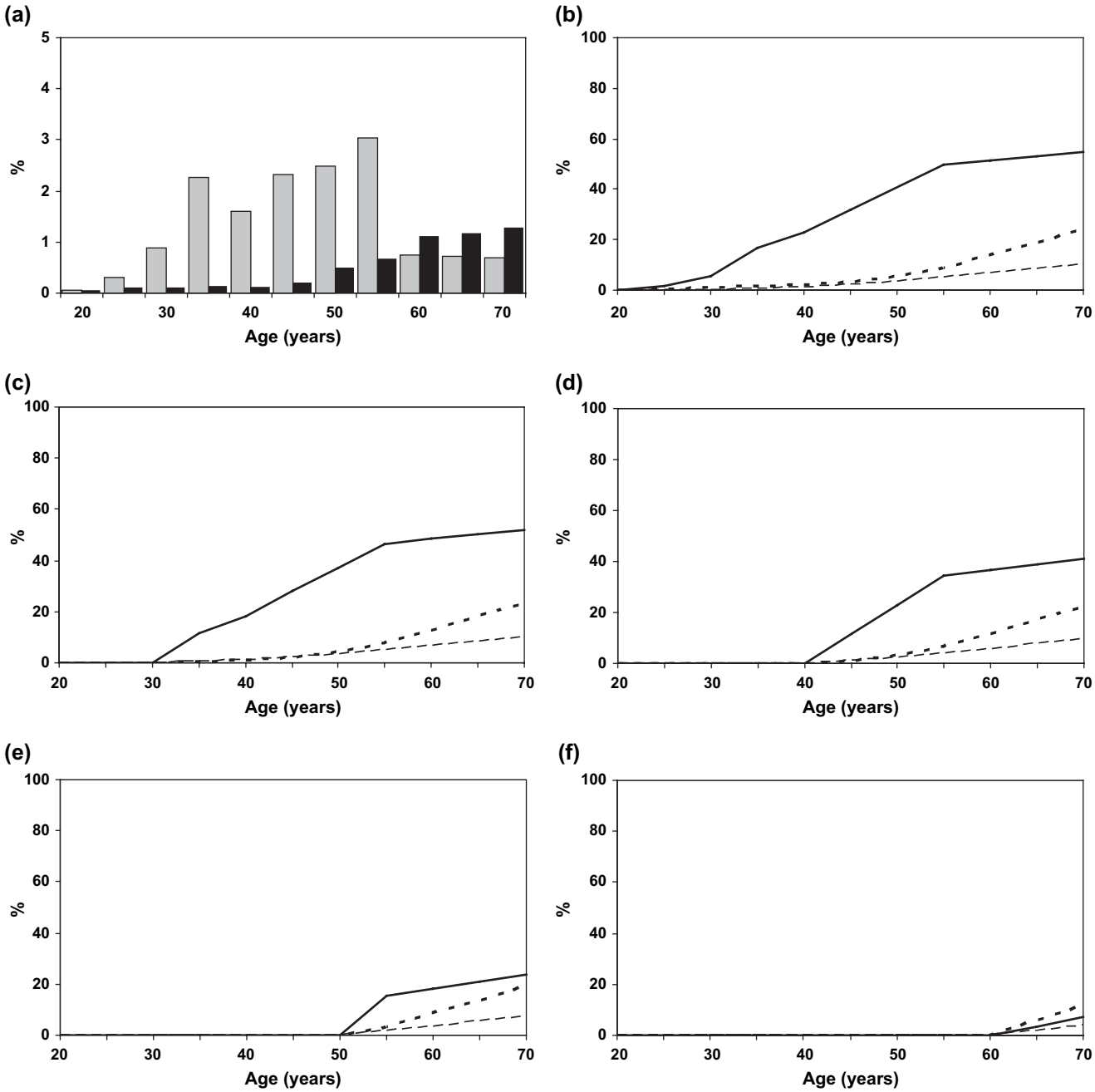

Fig. 4. Short-term and long-term risks of cancer in BRCA2 carriers. (a) The age-specific risks of breast (□) and ovarian (■) cancer (risks per woman per year, that is 'short-term risks') for an Australian female BRCA2 carrier are summarized. The remaining figures present the cumulative risks (i.e. 'long-term risks') of breast and ovarian cancers for an unaffected female BRCA2 carrier of different ages; in each case, the cumulative risk of breast or ovarian cancer (combined) for an unaffected woman in the general population is shown for comparison. (b) from 20 years, (c) from 30 years, (d) from 40 years, (e) from 50 years, and (f) from 60 years. ——, breast; - - - , ovary; – – –, population (breast and ovary).

personal and familial factors that must be addressed in considering any approach to reduce a woman's risk of cancer in this setting.[10] For example, the family's experience of breast versus ovarian cancer and the ages at diagnosis has an influence on the risk that an individual carrier will develop a certain cancer by a given age.[11]

Nonetheless, it is hoped that presenting these data as both short-term and long-term absolute risks for carriers of different ages may facilitate counselling by health-care professionals and decision-making by the women involved. Leaflets that incorporate Figures 3 and 4 have been developed for patients and are available on request.

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